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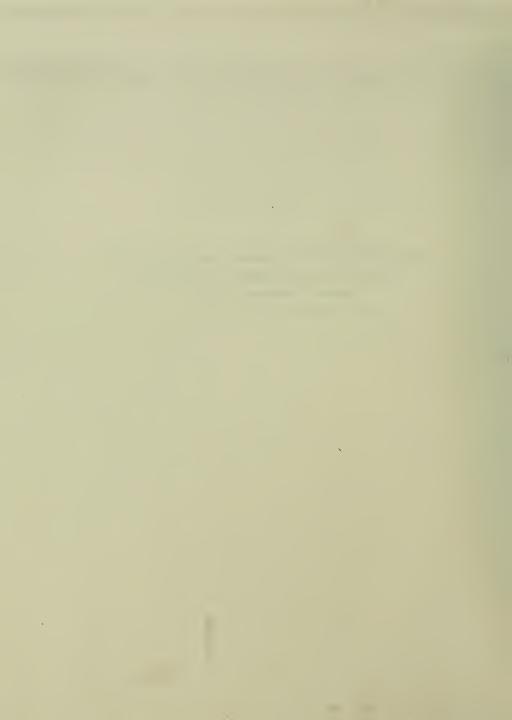DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

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PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Report of Program Activities

July 1, 1974 through June 30, 1975.

ANNUAL REPORT

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OFFICE OF THE DIRECTOR

This Director's Summary highlights some of the Division's FY75 activities, and provides a perspective in which to see the progress of computing at NIH, as you read the details of what the DCRT Laboratories and Branches did this year.

Ten years ago the new Division of Computer Research and Technology was organized on the NIH campus. Today computing has become an integral part of the NIH scene, and literally involves and affects work of thousands of scientists and administrators. The key to this integration is the interaction between those who provide computing capabilities and those who use these for biomedical research, health administration and program leadership at NIH.

To be useful and successful any such interaction must involve:

- a worthwhile information processing task
- a successful computer system
- a way to perform the task on the system.

Successful Computer Systems

NIH has successful computer systems, largely because NIH planned for and was willing to build its own centers of technical expertise. As a minimum, successful computer systems must be both reliable and accessible. This requires expertise in computer hardware, computer software, and electronic communications, plus an ability to combine all three appropriately for the tasks at hand.

The DCRT Computer Center Branch continues to provide NIH with responsive, reliable computer services and facilities of an unexcelled quality and diversity. To provide computing power to some 5000 users is no trivial matter. The CCB success derives largely from recognition that the key to developing a good central computing utility is high quality system software expertise, (system programmers).

The CCB report therefore emphasizes this competence and describes several improvements which balance an average of more than 10,000 computing tasks per day among several large, interlinked computer processors, while handling 80,000 on-line data sets and archiving almost 30,000 reels of computer tape. In this context, one can see the importance of the implementation of the automatic data migration facility, the automatic tape inventory and registration, the "quick" and "discount" services, and various privacy protection facilities.

These improvements carry forward the CCB philosophy of an integrated utility, based upon reliable commercially available hardware and accessible through reliable commercially available commmunications lines. Perhaps the greatest tribute to the CCB system teamwork is the recognition and emulation it receives by professionals outside the NIH, including those who provide commercial computing services.

The DCRT Computer Systems Laboratory must be viewed from another perspective since its mission and activities focus on computing tasks of a different type. It develops systems tailored to needs that cannot be met by a central computing utility. These needs fall largely in biomedical research laboratories and in clinical care areas that have requirements for real-time data collection, analysis, display or process control, as well as an interactive computing capability for research and clinical staff.

As noted in previous annual reports these tend to be longer range projects. Indeed, two of the more significant CSL projects get little discussion this year because they are not "new." One is the continuing work on systems for fundamental biochemical and biophysical investigation among the NIAMDD laboratories in Building 2. The other is the expansion and refinement of the system supporting the NHLI Intensive Care Unit.

The CSL summary notes that in addition to software competence its work involves considerable electronic engineering expertise. The intricacies of computer hardware and of directly-wired communications lines are an inescapable part of specifying or designing CSL systems. Many of these involve the acquisition, conditioning, and preprocessing of complex signals from instruments in the laboratory or at the bedside. The CSL staff too has its share of recognition and emulation by professional colleagues outside of the NIH.

Worthwhile Information Processing Tasks

There are three salient facts about the value of information processing tasks at NIH.

1. Judgements about their value rests primarily with those persons, scientific or administrative, who use the information products as part of their work, and secondarily with those who must evaluate that work.

2. The value of doing an information processing task on a computer involves a separate judgement but this also must rest with the same people who make judgements about the value of the task itself, although DCRT often provides advice.

3. Computing at NIH has flourished because there are large numbers of worthwhile information processing tasks at NIH and many of these are worth doing on a computer.

Biomedical research is, after all, a matter of acquiring and evaluating new information in the light of existing knowledge, and health science administration involves the evaluation processing of large amounts of information about research and training projects. Behind both NIH research and administration lies the considerable logistical and managerial infrastructure inherent in operating a complex organization consisting of thousands of people responsible for many hundreds of millions of dollars.

The activities of three parts of DCRT provide examples of some worthwhile information processing performed on computers.

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The Physical Sciences Laboratory studies problems in physics and chemistry that relate to biological sciences. These investigations look at fundamental levels of biomedical phenomena. In general they entail theoretical studies and experimental work on interactions among molecules or the interactions of molecules or other small entities with a variety of physical force fields, e.g., centrifugal or electromagnetic.

Like much of modern physical science, the PSL work uses the precision of mathematical forms for the theoretical studies. It uses the power of computers both for numerical evaluation of mathematical statements and in experimental work as part of sophisticated instrument systems that automatically measure the changing response of the material under investigation and in many cases automatically change the force fields.

But significantly, the PSL has been rather frugal in its use of computers. In many instances it uses programmable calculators rather than full-blown computer systems because its competence in mathematics permits PSL to make appropriate simplifying substitutions in place of more complex forms. As the PSL report indicates, this mathematical talent is applied in a variety of collaborative studies with scientists outside of NIH, and the laboratory sponsors occasional meetings of experts on pertinent topics.

The Laboratory of Applied Studies operates in a similar mode with respect to problems closely related to clinical research and care. Some studies involve mathematical theory and numerical analysis, or develop statistical theory and methods for analyzing clinical data.

Others deal with complex clinical information forms such as electrocardiograms and radionuclide scintigraphs, the X-ray like images produced by the radiation emitted from minute amounts of radioactive substances administered in diagnostic tests.

Such statistical and clinical studies may involve a considerable amount of mathematical computing. They also make use of a computer's ability to organize, store, and retrieve sets of data precisely and efficiently, as well as to control the acquisition and/or conditioning of the electronic signals from which the data are derived.

Hence, it is no surprise that both LAS and PSL work with the Computer Systems Laboratory and other NIH institutes on projects which require the development of specialized computer systems and at the same time make use of the facilities of the Computer Center Branch for large scale data processing and computation.

The DCRT Office of Administrative and Management Services contains examples of the value of computing in administrative data processing. Perhaps the best example is the DCRT Project Accounting System, which handles the accounts for all DCRT services that are billable through the NIH central accounting system under the NIH Service and Supply Fund (the Revolving Fund). The system was designed by members of the Computer Center Branch and Data Management Branch. It automatically collects data on all jobs run on the CCB computer utilities and is fed supplementary information on other billable personnel, rental and service charges.

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Those data are available at all times for "emergency" on-line queries. Each month's charges are billed by transfer of data on magnetic tape to the NIH Office of Financial Management. The system also makes microfiche copies of the monthly bills for ready visual reference if questions arise.

The information thus processed is absolutely essential for responsible fiscal management under the service and supply fund. Note that in this case the computer is essential for recording measurements of its own activities. It is also valuable for keeping files well organized for query and for easy transfer to other computer-based accounting systems. The microfilm records supplement and reduce the need for costly on-line inquiries.

Performing Worthwhile Tasks on Successful Systems

The mere existence of successful computer systems and worthwhile information processing tasks does not guarantee that the tasks will get done.

The DCRT tasks mentioned above benefit from close proximity within DCRT to programmers and information specialists as well as to successful computer systems.

But many computer users at NIH do not have all this talent available "down the hall." Their initial interaction with computers usually occurs first through DCRT staff and then directly through the variety of facilities which are provided and supported by the DCRT staff.

These facilities are computer programs designed to make it easier to create new programs and to use them. Indeed, this very concept of computer programs interacting with each other as well as information and people and computer hardware is absolutely essential to an understanding of modern computing.

The Data Management Branch uses many such facilities to provide practical solutions for the variety of data processing problems posed by NIH scientists and administrators. One key to the DMB success is its ability to employ, as needed, a full range of such facilities: conventional compiler-based languages, conversational programming systems and the data management program generators that DMB itself has created. During the past year DMB has improved its generators and plans to have a completely revised system available early in FY1976.

The Clinical Information Utility System segment of the DMB Clinical Center Project is an excellent example of the accomplishments which are possible through continuing interaction of knowledgeable staff in DCRT and other organizations. The CIU System addresses a long felt need for rapid, accurate and controlled retrieval of subsets from the wealth of data accumulated by the Clinical Center clinical laboratories over recent years. Development of the system involved resolution of many of the classic jurisdictional ard privacy issues which appear in articles about data management in large organizations.

As in previous years, the DMB summary includes a number of projects in support of clinical research with the various NIH institutes. An excellent example is the retrospective NHLI study of pre and postoperative data on more than one thousand cases requiring surgical replacement of heart valves.

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The DMB report also demonstrates a strong support for NIH laboratories and administrative areas. In the latter, a close look at the project list shows their work interacting productively with the central systems maintained and operated by the NIH Division of Research Grants and the NIH Office of Administration.

The Laboratory of Statistical and Mathematical Methodology is a counterpart to DMB. It provides practical solutions for problems involving the statistical analysis and mathematical evaluation of data. Like DMB, LSM uses a full range of facilities: compiler-based languages, interactive systems, a variety of statistical packages developed elsewhere and two facilities, MLAB and MODELAIDE, by DCRT staff members who are now part of LSM.

Here again success is a result of the interaction between the expertise of LSM and the NIH scientists and administrators who have information processing problems. The examples listed in the LSM report show that these consultative and collaborative efforts have flourished during the first year of the laboratory's activities.

The close reader of the DMB and LSM reports may note that DMB has several projects involving statistical analyses. Some of these are projects started in DMB years ago and have built up a close working staff relationship. But it is more important to realize that information processing tasks associated with sets of data do not fall into two discrete classes.

Thus, while LSM is a DCRT focus for certain statistical and mathematical disciplines, these are found elsewhere in DCRT. Similarly the research activities of LSM in size and shape and pattern recognition, computer science and various branches of mathematics have direct or related counterparts in DCRT. Without this commonality of expertise among the DCRT labs and branches much of the collaborative multidisciplinary work within DCRT would suffer.

DCRT Training Courses and Seminars are another essential element in getting the worthwhile tasks done on the successful computer systems. In many ways it is useful to view the NIH Computing System (the machines, the software, the computer science and information science expertise and the NIH staff with information processing tasks) as a learning system.

This view leads to two questions. Who needs to know what about the theory and practice of information handling and computer systems in order to achieve the best research, administration and program leadership? What kind of "educational experiences" are needed to provide that knowledge and the skills and attitudes which enable the knowledge to be used effectively? The first question tends to be answered throughout NIH by each person for his or her own perceived needs. The second is answered rather well for the specific DCRT supported programming languages and facilities by training courses given twice a year.

Future Progress of Computing at NIH

The progress of computing at NIH has followed the major outlines of the scenario envisioned in the early 1960s. Then, after a year long study (1962-63)

NIH opted for a new Division of Computer Research and Technology. This divi-
sion was to be a strong central computing utility and programming resource,
embellished with laboratories of excellence in computer systems engineering
and mathematics. All of this came to pass.

Socalled Data Base Technology has made slower progress. There was to be
a Data Systems Analysis and Design Branch in the original DCRT. The Federal
enthusiasm of the late 1950s and early 1960s for central pools of systems
analysts separate from computer programmers never materialized at NIH. This
was due in part to the nature of NIH and in part to the state of computing at
NIH and elsewhere.

There was no NIH centralization of administrative data processing systems.
A group of systems analysts has functioned within the Division of Research
Grants, Statistics and Analysis Branch, which operates its centralized data
management systems for grants and lately for contracts. The Office (now
Division) of Financial Management has in large measure obtained systems anal-
ysis, design and implementation by contract.

In spite of some promises of the late 1960s there never developed a good
commercial general purpose information processing system to apply to data
management. To fill the void the Data Management Branch developed a data
management system for its customers in the various NIH Institutes and adminis-
trative offices.

More recently there have emerged on the market some data base management
systems which begin to approach the facilities promised in the 1960s. It
remains to be seen whether they will be suited to the NIH needs and whether
the central NIH administrative data processing functions are suited to the
concepts of integrated data base management.

Federal Automatic Data Processing regulations (ADP) still haunt computing
at NIH in the form of the GSA. The general problem was discussed obliquely in
last year's Director's Summary, with a historical note to show recognition in
1963 of the difference between NIH computing needs and those previously envi-
sioned by Federal ADP philosophies. Whether or not current differences can
be resolved is a matter of some concern for the future of the NIH central com-
puter facilities.

Several trends will affect computing at NIH. One is resource constraints.
The last seven years brought tighter employment ceilings to most of NIH and a
call for higher productivity throughout the Federal Government. To the extent
that computers can increase the "efficiency and effectiveness" of NIH and
other Federal employees, we are likely to see greater use of systems like the
NIH Computer Center, which are reliable, accessible and relatively inexpensive.
The ultimate limit on expansion will be economic, depending on the values
placed on computing compared to other activities during a period of continuing
inflation.

Another trend appears in two areas which are not computers in the conven-
tional sense. These are electric calculators and "word processing machines."
The NIH property rolls currently list some 3200 "electric calculators" ranging

from $35 manual calculators to $12,000 programmable calculator systems, and the NIH rents or leases some 390 magnetic card or magnetic tape typewriters.

Programmable calculators are now available with cassette tapes and with alphabetic characters to put labels on printed results (and presumably on program statements). "Communicating" mag card and mag tape typewriters are available which send and receive messages via telephone lines, linking to the NIH central computer (or in theory to any other compatible computer in the world with telephone posts). And new product lines are announced monthly.

The significance of these trends to computing at NIH will be evolutionary rather than revolutionary. The need for a central NIH computer system will not disappear. Nor will every office and laboratory demand its own complement of number and word processing machinery and "intelligent terminals" linkable to a large computer. What will emerge is a more diverse information processing environment and a more sophisticated body of information processors (people) within NIH.

The challenge to NIH and hence to DCRT a decade ago was to make computers available and reliable. This has been met. The challenge for the decade ahead is to help computing in its increasing variety become more effective and productive as part of the "information intensive" environment of NIH. To this end one can foresee increasing, not decreasing, interaction between DCRT expertise and scientific and administrative staff as well as with policy-making groups at NIH and elsewhere.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT

2. OFFICE OF SCIENTIFIC AND TECHNICAL
    COMMUNICATION

3. William C. Mohler
    Director

This year DCRT established a new Office of Scientific and Technical Communications. The office formally brings together the DCRT Library and the Scientific and Technical Information Office and also is a locus of collaborative and research projects in information science and mathematics.

One domain of the office is information about information processing. Its concern is the adequacy of information reaching NIH scientific staff about computers, about their applications to scientific and administrative problems and about the DCRT activities. Another domain is application of advanced information science principles, including mathematics, to multidimensional information structures.

The office is small as well as new. Its three areas are led by Judith Prewitt, mathematician and expert on image processing, Ruth Ketler, the DCRT Scientific and Technical Information Officer, and Ellen Chu, the DCRT Librarian. Two part-time staff members and two co-workers from the Data Management Branch constitute the rest of the group. The Chief of the office is the DCRT Associate Director in a dual position.

The DCRT Library serves three functions. It is an integral working part of DCRT activities, a resource for the NIH staff, and an independent member of the network of special libraries in the Washington area. This is reflected in the 1974 circulation statistics. Some 60% of the books are borrowed by DCRT staff but over 60% of its more than 300 borrowers work outside of DCRT.

To meet these needs the library added about 230 books, 100 technical reports and theses, and 25 new periodicals this year to its collection on computer science, mathematics, engineering and related topics. It also instituted a review of holdings and subscriptions to eliminate outdated and unused materials.

As part of the library network, the DCRT library continued to include its catalog cards in the NIH Library catalog, to provide MEDLINE bibliographic services and to arrange for bibliographic searches through the NASA Scientific and Technical Information Facility and the Defense Document Center.

During her first year as librarian, Mrs. Chu has made several changes to improve effective service and operating efficiency, based on her questionnaire survey of library users and on the advice of her ten member DCRT Library Committee. For the coming year she ambitiously proposes: 1) a complete inventory of the collection, 2) an update of the catalog, shelf list and journal holdings list, 3) modifications to the automated circulation list, 4) improvements in

the work area and library layout, 5) investigation of microform reading equipment, and 6) revision of the reference collection. She also plans further cooperative efforts with other local libraries.

The Scientific and Technical Information Office began to enlarge its scope this year. It initiated new steps to analyze the needs of the NIH staff for information about computers, about their applications and about DCRT activities. A questionnaire survey of some 500 NIH laboratory, branch and department chiefs and administrative officers disclosed a broad expression of interest in, or need for those three kinds of information. This response is indicative of the extent to which computing has generated application and interest in all parts of NIH.

The new STI Officer, Mrs. Ketler, arrived in the midst of the DCRT preparations for the Alumni Reunion, the Public Open House and the Bicentennial Exhibit. In conjunction with the Computer Systems Laboratory and other members of DCRT, she helped to implement an exhibit about computing at NIH incorporating a slide show with sound track and a supplementary brochure. In addition to the exhibit DCRT presented five examples of computing via remote terminals to demonstrate the broad capability of human interactions with computers, by such means as graphic displays and audible responses including computer-generated speech.

During the fall, the STIO assisted the Computer Systems Laboratory in preparation for a conference on Computers in Cardiology which was sponsored by DCRT in conjunction with NHLI, The European Congress of Cardiology and the American IEEE.

As in previous years, the Scientific and Technical Information Office answered many queries from both inside and outside the NIH. The majority of these requests were for technical reports, for specific software programs and for information about computer applications. The office continued to handle a number of information reporting functions required by Federal regulations.

In the coming year, the office plans both to better define the interests and needs expressed in this year's questionnaire survey and to develop a set of presentations to meet them.

The work on multidimensional information structures has several dimensions. Mrs. Prewitt has been a leader as well as a collaborator in programs of three divisions of the National Cancer Institute. These include development of new techniques for diagnostic radiology, advances in automated clinical cytology, and analytic studies of subcellular cell and tissue characteristics of several types of neoplasms. On the NIH campus she has begun several collaborative projects in data analysis with scientists in the National Heart and Lung Institute.

Her active participation in these programs entailed many site visits and conferences. She was also an invited speaker or participant at some two dozen conferences, seminars, and workshops in the United States, Europe and Japan. These all related to her interests in development of rational bases for utility and effectiveness of both diagnostic and therapeutic procedures.

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The Office of the Assistant Director, DCRT, provides three basic capabilities:

1. The Office serves NIH as the focus for coordination of ADP
    policy matters and thus also as a central point of NIH
    contact with PHS, the Office of the Secretary, other DHEW
    agencies, GSA and OMB for NIH ADP policy questions and
    relative to NIH participation in the development thereof.

2. The Office supports the Director of DCRT by providing a
    point of reference and coordination to insure that DCRT's
    own ADP activities are consistent with NIH, PHS, O/S,
    GSA and OMB policy directions, and

3. The Office supports the Directors of DCRT and NIH by
    providing advice on ADP resource acquisition and allocation
    necessary for DCRT and NIH mission performance.

During the year the role of the Office of the Assistant Director, DCRT, as
the NIH-wide coordinator of ADP policy needs and its role as the central
point of contact on ADP policy questions with PHS, OS, OMB, GSA and other
Federal Agencies was given added status by its formal recognition as the
Office of ADP Policy Coordination. This change solidifies the role of the
Director, DCRT, as the principal advisor to the Director of NIH on all ADP
matters. This is also a first step in the implementation of the organiza-
tional alignments recommended by the AMETA Study of 1973.

A major continuing undertaking started during FY72 and continuing thereafter
is the technical and management leadership in development of NIH's annual
ADP Plan. This plan attempts to lay out a two year projection for ADP
equipment, manpower and ADP support contracts for all components of NIH.
This planning process creates an orderly opportunity for ADP users to take
stock of their goals and accomplishments. The most recent annual plan
covered NIH ADP efforts exceeding $34 million for FY75, $34 million for FY76
and $38 million for FY77. Through extensive coordination with PHS and the
Office of the Secretary, the office was able to integrate several GSA and OMB
reporting requirements into the NIH ADP planning process, thereby reducing
the administrative burden which would otherwise be entailed in the current
trend toward "overmanagement" of ADP.

In serving as a central point of contact for NIH on ADP related matters with
PHS, DHEW, GSA, OMB, etc., a large number of NIH research and research support
staff members are spared the agony of becoming expert in the many nuances of
ADP related regulations. Since these regulations are generally written from
a second generation business data processing point of view, a thorough
understanding of their purpose and operation often allows beneficial
interpretations of their application to the NIH research environment.

During FY75 the ever-increasing "overmanagement" of ADP by OMB and in particularly GSA, has resulted in the need for the Office of the Assistant Director, DCRT, to spend an ever-increasing percentage of available man-hours on the paper work associated with ADP procurements. Notwithstanding the increased burden of paper work, the office has been able to make technical contributions which have assisted the National Library of Medicine in making an orderly upgrade of the MEDLINE capabilities and assisted the Clinical Center in the installation of a new clinical chemistry system and in the selection of a total Hospital Information System. In addition, numerous small laboratory computer systems have either been installed or placed on order. In each case the office provided both advice and assistance with regard to procurement and policy considerations as well as technical advice.

The NIH policy coordination role is exercised in part by review of all NIH proposals for contracts or procurement actions involving ADP equipment, services or programming which must all be cleared through this office prior to being executed. This provides a continuous opportunity to alert program or contract officials to opportunities to avoid duplications, reduce costs or, importantly, to avoid difficulties with higher echelons.

With regard to the role of assisting the Director, DCRT, with technical coordination of internal DCRT operations, the office provided technical leadership with regard to two major physical plant undertakings initiated during FY75. The office coordinated an architectural and engineering study which will eventually result in the conversion of the second floor of Building 12 into space usable for computing equipment. This innovated approach to overcoming the natural limitations of the size of a building will, when brought to fruition, result in the novel but functionally effective concept of a two-floor computer room. Secondly, during the year the office coordinated for Engineering Design Branch the ADP technical aspects of an entirely new building, 12B, which will allow for expansion of the computation-al functions of the Division.

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Automated Processing of Medical Language

Previous Serial Number: 4.9

Principal Investigators: A.W. Pratt, M.G. Pacak

Other Investigators: P. Graepel, G. Dunham, S. Harper,
                                  M. De Meyts-Graitson
Man Years:

  Total: 2.5
  Professional: 2.5
  Other:

Project Description:

  Background:

    For the past several years, an effort has been underway to develop a
    linguistically-oriented system for automated processing of medical
    language, and the program for information storage and retrieval of
    pathology data. The system includes the acquisition of textual
    information, the interrogation of a medical dictionary (SNOP), a set
    of transformational morphosyntactic and morphosemantic rules which
    are required for the identification of the information content of the
    input messages. The system for automated indexing of pathology data
    became operational in 1971 and is going to be extended to other
    subfields of medicine.

  FY 74-75 Activities:

    Development of a procedure for automated morphosyntactic analysis of
    medical language. The program was written in RMAG and PL-1 and is
    fully operational.

    The model for the construction of a computer-oriented medical micro-
    glossary for cancers and the design of a semantic model for the
    interpretation of medical records are being tested.

    A program for automated encoding of French pathology data was developed
    and successfully tested. This program is compatible with the program

which was developed for the encoding of English pathology data which became operational in 1971.

Preliminary design of lexical processor and manipulator for study, comparison and maintenance of medical lexical material. Feasibility trials for the implementation of the lexical processor indicate that NIH 370 system would serve as a base.

A program was developed for the identification and transformation of terminal morphemes in medical French (M. Graitson) which became a part of the French medical encoder (see appendix).

Analysis of a set of German language autopsy reports in preparation of an automated preprocessing method for medical German. Special attention was given to the problem of segmentation of compound words in German (Dr. Graepel). The preliminary results of the segmentation algorithm were used for the development of a statistical model for word segmentation by Dr. Mosimann and C. Clark.

Future Efforts:

Improvements of English and French encoders on the syntactic and semantic levels (development of paraphrasing rules, classification of semantic operators, etc.).

Construction of computer-oriented microglossaries for tumors and cardiology.

Application of statistical linguistics to medical data processing, and the construction of medical dictionaries.

Publications:

1. Pratt, A.W.: Medicine and Linguistics, MEDINFO 74, North Holland Company (1974).

2. Pratt, A.W.: Representation of Medical Language Data Utilizing The Systematized Nomenclature of Pathology, Proceedings of Symposium "Computers in Laboratory Medicine, Univ. of California, San Francisco, February 1975.

3. Pratt, A.W.: Organizing the Medical Data for Pattern Generation, Proceedings of IRIA Medical Data Processing Symposium, Toulouse, France, March 3-5, 1975.

4. Pratt, A.W.: Computer-Based Information System for the Research Environment, Proceedings of IRIA Medical Data Processing Symposium, Toulouse, France, March 3-5, 1975.

5. Pacak, M.G.: Computational Linguistics and Information Handling, Management of Information Handling System, ed. P.W. Howerton, Hayden Book Co., New Rochelle Park, N.Y., 1974; pp. 19-47.

PUBLIC HEALTH SERVICE-NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1.   DCRT-2
     Serial Number

2.   COMPUTER CENTER BRANCH

3.   J. D. Naughton
     Branch Chief

MISSION

The Computer Center Branch designs, implements and operates a
large general-purpose computer utility to meet most effectively
the dynamic and diverse requirements of both N.I.H.   research
investigators and managers in the support of modern medicine.
This charge includes the original development of new system
facilities to meet the unique requirements of the NIH mission in
order to bring the full power of the computer to bear on
problems at every level of biomedical research in many remote
locations.   The core of this computer utility is a network of
computers and remotely located terminals, which, by means of a
modern communications network, extends the power of the computer
directly into research laboratories and administrative offices
throughout N.I.H.   This provides immediate access to the
computer thus minimizing delays in the research program and
making more efficent use of critical manpower than more
traditional methods. An inherent responsibility of the Computer
Center is the continued research and development of new methods
to extend the network even further into the research environment
while continually adapting to the constant impact of new
knowledge and program direction.

A full spectrum of computational services is provided to all
Institutes and Divisions of the NIH on a fee-for-service (cost
recovery) basis.   These facilities include conversational
programming, graphics, microfilm output, text editing, remote
job entry, time sharing, data base management and batch
processing.   Large systems as well as mini-computers and
terminals are tied together providing a "distributed capacity"
available at many levels.   Research into the computer and
information sciences coupled with close cooperation between the
N.I.H. medical investigators and the computer scientist have
introduced computers directly into the research environment
where they can perform most effectively in attacking the complex
problems of medical research.

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The medical research programs of N.I.H. require the most powerful and flexible of computer services and tools available today. The computer network provided must have a distributive power that is easily accessible when needed to scientists in the laboratory itself. The goal is to mold, polish and, in general, enhance the computer into a complete tool for medical research and its administrative support. New areas of computer applications are sought out continuously in conjunction with a comprehensive training program to inform research investigators of the latest methods in the use of computers to most effectively meet the unique requirements of their individual laboratories.

1974 ACTIVITIES

In spite of a general upwards spiraling of costs throughout the country, the NIH Computer Center began the year with the announcement of the most significant rate reduction ever offered NIH computer users. Rates were reduced 22.8% for all work processed on both the IBM System 370 and the DECsystem-10. In addition, the Night Service discount rate was increased to 25% for all work processed between the hours of 6 p.m. and 8 a.m. Increased workload, larger computer systems and internal modifications to the operating system resulting in improved system performance, combined to maintain the lower rates throughout the year in spite of continually increasing operating costs.

As the effects of the manpower shortage continued to become even more acute throughout NIH, many areas turned to "automation" as a means of compensating for decreased manpower without curtailing programs. Existing computer programs were modified or extended to accommodate new applications and entirely new programs were designed and implemented specifically to automate procedures that had previously been done by hand. As a result, the demand for computer services from the Center continued to increase dramatically throughout the year. Total workload increased 25% to 205,000 jobs/sessions processed per month. Interactive terminal systems provided service to 3000 sessions daily and the number of on-line disk datasets increased to 80,000 while the printers produced over 150 million lines of printed output per month. NIH is undoubtedly the most "automated" Agency of the Federal Government.

Two new processing services, "discount" and "quick" were introduced this year. These services were designed to encourage the shifting of workload from the peak load period during the daylight hours to overnight service. Users electing to use the discount service have their jobs automatically held until after

6 p.m. when the job is run at a 25% rate reduction. This has a double effect in that it also improves turnaround time for all daylight work and reduces the user's cost for computing services. Quick service, on the other hand, provides a facility to insure fast turnaround for users who choose to work at night. Through the quick service, jobs submitted during evening hours are run ahead of the large overnight production runs, thereby eliminating the long waits and making the user's time much more productive. Quick service also receives the night-time discount.

Because of the increasing national concern for personal privacy and the security of information stored and used in computers, the Computer Center designed and implemented a number of security improvements for the NIH Computer Utility. Most significant of these was the development of an automatic data encoding (scrambling) facility which is usable in all languages and from all systems supported by the Center. This facility permits a user to easily encode sensitive data in such a way that even the Computer Center could not decipher it. In addition, "keyword" protection became mandatory for both batch processing work and interactive terminal sessions while access to registered initials and account numbers was restricted. Additional facilities to further insure the confidentiality of sensitive data and the physical security of the Computer Center itself were designed and implementation was begun.

Many new or improved software services were introduced this year. The Integrated Plotting Package provides the user with a mechanism to generate intermediate text which will be processed, possibly after storage on an external file, by a variety of different plotting devices.

The Extended Printing Facility which provides a convenient means of printing mathematical expressions containing superscripts and subscripts as well as greek letters was improved to provide additional function and convenience for the user.

This year saw many improvements for TSO users, especially in the area of performance. After a slow start, internal systems software and hardware modifications brought TSO response up to an acceptable level. A new function gave users the ability to monitor CPU time used during a TSO session. With this facility users had more control over their terminal environment and "runaway" TSO programs became a thing of the past.

Many additional internal system changes were made that were transparent to the user, except that the changes increased the efficiency and reliability of the system and therefore either improved turnaround time or kept it from increasing as the

workload grew. The disk accounting system was modified to improve internal performance and provide more effective dataset recovery facilities. As the size of the tape library increased to over 27,000 reels, an automatic tape inventory and registration was implemented. In addition to insuring more accurate handling of tapes and reducing the manual burden for machine operators, this facility consolidated the "Tape Listing" and "Dataset Listing" into one convenient report for users.

The usefulness and popularity of many of the software systems and improvements designed by the NIH Computer Center was illustrated by numerous requests for copies received from other facilities throughout the world. Over 150 copies of software packages such as SHARED SPOOL, WYLBUR, DATASET MIGRATION, SPOUT, HASP, OCR, COM etc. have been distributed to federal and state governments, academic institutions and commercial organizations. The superiority of the Shared Spool package over other ways of controlling multiple CPUs was illustrated when IBM announced Multiple Access Spool, which is their version of the NIH Shared Spool System.

The DECsystem-10 was expanded to meet the demands of the workload which increased throughout the year. April 1, 1974 saw the addition of a second KI-10 CPU as a slave processor. The dual master-slave KI processors have provided the increased capacity needed to maintain excellent time-sharing services as well as CPU redundancy assuring continued service in case of failure of one processor.

The rapidly accelerating use of this system for time-sharing, laboratory-oriented programs, graphics problems required a continuous enhancement of both the software and hardware of the DECsystem-10. Plans were developed to provide additional on-line disk storage capacity and improved magnetic tape drives for this system next year.

Selection of the NIH Computer Center as one of two test sites for advanced monitor software paid dividends in terms of increased system reliability and early availability of new features, e.g., virtual memory.

The telephone line capacity of the DECsystem-10 was increased to 41 lines thus reducing the frequency of busy signals experienced by users. In addition, this year saw the introduction of support for 2741 terminal users by single-digit dialing on the NIH dataswitch.

A very stable version of the SAIL programming language was introduced and generated very few problems. A new Fortran compiler with excellent optimization was added to decrease

running time for compute-bound programs. The double-precision hardware features of the KI-10 processor further helped decrease execution times.

Dataset controls were added to improve the computer's handling of dial-in telephone lines. With the dataset controls, the computer detects when a telephone connection has been broken and suspends or detaches the session. The line is then re-initialized and freed for the next caller.

Omnigraph, the graphics system on the DECsystem-10, has been extended and improved both to achieve more efficient utilization of the entire computer system and to provide more flexible facilities. The Omnigraph system was modified to allow the executable code of large Omnigraph programs such as MLAB to be shared among many users. This has resulted in a saving of as much as 150K core at a time. In addition, new routines were added to facilitate the use of vertical text and raster mode on the DEC340 display. Support for the new DEC Fortran, Fortran-10, was also implemented.

TXTCOM, an additional microfiche package, was made available to DECsystem-10 users. This package provides ASCII characters not normally available, giant lettering of file titles and index lettering across the top of the fiche. The transfer of data files between the DECsystem-10 and the IBM370 System was made even easier by the development of several 370 catalogued procedures, which are used with corresponding DECsystem-10 command files and the EBCDIC program. In addition, a new operational procedure was implemented to aid in the physical transportation of tapes between the DECsystem-10 and the System 370.

Changes in both the System 370 and the DECsystem-10 required significant revisions to Computer Center technical documentation to update and describe new standards and facilities. The Computer Center Users Guide was updated while new editions were issued for the NIH TSO Command Reference Manual and the WYLBUR Reference Manual. Documentation revised during the year included: the CPS Basic Primer, RHB Routines, the DECsystem-10 Timesharing Guide and DECsystem-10 Display Systems Manual. In addition, the MLAB Manual was revised, and three new RMAG manuals were published.

The Technical Information Office was kept busy distributing these new manuals as well as those provided by vendors. Altogether, 35,646 pieces of documentation were distributed to users of the NIH Computer Center during the year. Most distributions were done through the Automatic Documentation Service which served the needs of 2,606 customers whose

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individual documentation profiles are kept on-line by the office.

The PAL unit, the interface between our users and the Computer Center, continued to provide aid and assistance to the 4500 registered users of the Center. Individual assistance to users, on specific problems, was given over the counter, by telephone (in numbers too numerous to count) and by written responses to 2000 Program Trouble Reports (PTRs). A new PTR facility was developed called the "Remote PTR". This facility allows a user to submit a _Programmer_ _Trouble_ _Report_ by using the TSO interactive terminal system. This aid was developed to help in problem determination for remotely located users who need help but do not have convenient access to the PAL Unit facilities, and whose problem cannot be solved through telephone conversation. Between calls the PAL Unit wrote over 100 pages of technical information to users thru the "Diagnostics, Bugs, & Hints" section of INTERFACE, developed a new version of PALTAPE, contributed to numerous system reconfigurations and applied over 458 major fixes to the vendor supplied software to improve the reliability and efficiency of the Computer Utility. These changes were made with minimal effect on the user community.

The training activities of the Computer Center were in great demand in 1974. Forty-three different courses and seminars were given covering general purpose programming languages, operating systems, terminal systems, and special facilities and programming aids, etc. Over 2000 requests to train people to use both the System 370 and the DECsystem-10 were received this year. Although 82% of all requests for training were accommodated, it was, unfortunately, necessary to reject 364 applicants due to lack of staff.

The requests for the elementary training courses were particularly strong as more and more NIH researchers, administrators and clerical employees discovered the usefulness of the computer in their daily work. It was necessary to teach eight complete sessions of the two week "Introduction to WYLBUR for Administrative and Secretarial Personnel" course this spring and summer in order to satisfy the requests made during the spring of 1974. Even so, the number of requests received for this course is still far greater than we can satisfy.

INTERFACE, the Computer Center's vehicle of communication with the users, was published 8 times during the year, an increase of one from the previous year. 307 pages of documentation on all phases of computing were distributed in these issues.

To give complete coverage to all facets of computing a Diagnostics, Bugs, & Hints section for the DECsystem-10 was

added to INTERFACE this year. This, along with the regular Diagnostics, Bugs, & Hints section, provides the users with the detailed technical information necessary to process work using both systems. The Compleat Computor and the Programming Methods sections appeared regularly covering timely topics. The third Annual Index through 1974 was the last issue of INTERFACE to be published in calendar year 1974.

Since over 95% of all work processed by the NIH Computer Center is received via the teleprocessing network, the communication facilities of the system were improved considerably. Conversion from Model 2703 teleprocessing units to the newer more powerful Model 3705 teleprocessing unit was completed. These new units permitted the addition of more lines but more importantly led to the announcement of new teleprocessing services not possible with the displaced units. Autospeed came first, allowing 2741's and teletype terminals to use the same communication port at varying speeds up to 300 baud. The data switch was expanded to provide additional lines for WYLBUR and TSO users and also to provide 1200 baud service. Over 850 terminals are available for use with the NIH Computer Utility and the number of lines accessible to the system was increased to over 300 to handle the work load. The expansion of lines was timely since the number of daily interactive sessions passed 3000. New highs for the number of simultaneous users were established when WYLBUR reached 239 simultaneous sessions and TSO hit 38.

The major hardware change of the year was the replacement of a 370/165 and a 360/65 by a 370/168-MP. This increase in computer power was installed behind schedule, but its impact was soon felt as turnaround time returned to the limits normally expected by the Center and its users. The continual increase in workload necessitated not only an increase in computational power but also an increase in peripherals as twenty-two new tape drives and three 1500 lines per minute printers were added to the system. The need for additional on-line disk storage space was met by converting the Model 2314 disk units to Model 3330 units. The 3330 units have from two to four times the capacity of the older 2314 units and transfer data two and one-half times faster. The 3330 conversion started in July and was completed in early 1975. The transfer of over sixty thousand on-line datasets was accomplished with no interruption in service. With the completion of the disk conversion, the shortage of on-line space should be over. Data migration of inactive data sets continues to insure that disk space is always available for current active projects.

Directly addressable memory on the 370/145 was doubled to two million bytes. The additional memory will enable more thorough testing of the large software systems to be done independently of the main CPU's in the system.

As the use of microfiche as a computer output medium increased to over 5.7 million images per month, a second COM unit was added to the system. The ease of use of the system, the reduction of bulk and an interest in saving paper all contribute to the constantly growing popularity of microfiche.

Year end saw the last major hardware announcement, the availability and support of high speed CRT display terminals for users of the NIH Computer Utility. Operating at 120 characters a second, the CRT's will provide users with transmission speeds four times faster than previously available. In addition to new functional capability, the new CRT's offer shorter sessions (more efficient use of lines), and better data entry and editing capabilities. Using an attached hardcopy printer remote users will be able to receive more printed output at their location. The CRT is usable with all systems supported by the Center on both the System 370 and the DECsystem-10. Users will have little difficulty using the CRT with existing programs or designing new programs specifically oriented to the CRT as an input/output device.

As the year came to a close, a Request for Proposals (RFP) for a major equipment upgrade to the NIH Computer Utility to provide additional capacity to meet the projected workload over the next three years was written and forwarded to GSA for appropriate action.

1976 Plans

In order to provide effective computational support to meet the constantly changing and diverse requirements of the NIH biomedical research activities, the Computer Center maintains a continual program of expansion and development. In addition to a significant increase in computational capacity to support existing programs, the Computer Center plans to implement a number of new computational facilities and services in support of new research and administrative programs during the coming year.

To accommodate the increasing demand for service in a responsive manner, the processing power of both the IBM system 370 and the DECsystem-10 will be increased significantly.

Procurement actions, begun last year, should result in the exchange of a presently installed IBM 370/165 with an IBM 370/168-MP central processing unit. This will represent an increase of approximately 28% in raw processing power as well as provide the capability for operation under the newer Virtual Operating System. This change will also include a corresponding increase in peripheral devices. Additional disk drives will

provide more on-line storage capacity for data and programs; new communication facilities will allow interactive access to the system using high speed (120 characters per second) CRT terminals; additional fixed-head-storage devices will be installed to improve system performance and efficiency; and high speed tape drives will allow faster tape processing.

During the same period, the DECsystem-10 will experience an even more significant increase in computational capacity. Both of the present processors in this system will be replaced by faster and more sophisticated KL-10 units providing a 200% increase in processor power as well as the ability for directly coupled multiprocessor operations; a direct communications link (PDP-11) will provide for automatic on-line data transfer to and from the System 370; new disk drives will provide double the present on-line data storage capacity; new 1200 baud dial-up communication facilities will provide more effective access for remote timesharing users; and replacement of the existing tape drives will improve reliability significantly and will provide a dependable facility for transfering large volumes of data to the System 370.

The present graphics display equipment (AGT 30 & DEC 340) will be replaced by a more modern surface display unit(s) to facilitate molecular structure research and biomedical image processing.

A standard interface will be designed and built to permit the interconnection of laboratory computers to the central DECsystem-10 without requiring "special" software to accommodate the differences between various manufacturers' equipment.

A new higher resolution incremental digital plotter will be installed this year to replace the present obsolete plotter. In addition to providing finer plotting increments the new unit is twice as fast as present equipment and considerably more reliable. This should result in reduced turnaround time for plotter users as well as improved accuracy and increased productivity of the operator. Procurement actions to provide new higher speed interactive hardcopy terminals, portable interactive terminals, terminal plotter, communication line scramblers, and batch RJE terminals for computer users will be issued this year.

To accommodate the planned hardware conversion, major modifications to the physical plant will be initiated but will not be completed for several years. Although a long range architectural plan has been completed for a total renovation of the second floor of building 12 to provide sufficient environmental support facilities (power, air conditioning,

water) to house both major computer systems, only phase 1 will be completed during this year. This phase will provide only temporary facilities to house a small number of disk drives. A roof-top "penthouse" will be partially completed to provide additional chilled water and electrical generators required for the immediate hardware expansion planned for this year. The administrative processes necessary for scheduling and implementation of the overall renovation plan will be initiated this year.

New software facilities and services planned for this year will have an even greater impact on the effective use of the computer in support of the NIH mission.

A completely new version of WYLBUR, which has been under development for the past two years, will become operational this year. The new WYLBUR will provide a multitude of new functions designed specifically to meet the unique requirements of the NIH research and administrative programs. Its new macro processing facility will allow applications not previously possible and the document preparation features will permit more effective preparation of research manuscripts as well as administrative documents and reports. Multiple active files, an expression evaluator, more flexible file searching features, and many other new facilities will make NEW WYLBUR one of the most usable computational services available anywhere.

A newly designed MILTEN, a communication line handler, will provide software support for high speed interactive CRT terminal access to the system for the first time. In addition to providing forms entry, block text editing, multiple type fonts, and character sets, and communications across virtual address spaces NEW MILTEN can accommodate thousands of simultaneous terminal users and at the same time simplify operator interaction.

The most complex software conversion effort ever undertaken by the Computer Center, conversion from OS/MVT, Release 21.6 HASP 3.1 to OS/VS2, Release 3, JES2, will be started during this year and is scheduled to be completed 18 to 24 months later. This new "Virtual" operating system will permit larger programs to be developed/processed without the delay and overhead introduced by segmenting or overlaying programs. Improved system integrity and reliability will facilitate a more dependable service with fewer interruptions due to software failure. Dynamic address translation will permit more efficient use of critical system resources as well as more effective manipulation of user data on the basis of application requirements.

It is anticipated that the Computer Center will offer the service of a data base management system, IMS (Information

Management System) for the first time this year. This new capability will provide NIH with the ability to develop multiple transaction-oriented applications using large centralized, but independent, data files. Conversational applications may be developed and maintained independent of terminal/communication technicalities, input/output traffic, and terminal and program message switching. IMS also provides automatic journaling and checkpoint/restart facilities to provide maximum data base integrity and minimum "out-of-service" time. Extremely elaborate control mechanisms provide the maximum possible protection against unauthorized access to the system or modification of the data base. This system will be available only on a restricted basis during fiscal year 1976.

During the coming year a new version of the timesharing monitor will be installed on the DECsystem-10 to provide new function for users as well as improved internal system performance and reliability. This new software operating environment will provide a facility for interprocess communications which will result in more effective scheduling and control of the entire system. A more flexible software interrupt facility will permit dynamic switching among tasks and expanded virtual memory support will permit both the servicing of a larger number of simultaneous users and the development of larger applications programs.

Because of the plans for major changes in both hardware and software for both the System 370 and the DECsystem-10, it will be necessary to completely rewrite almost all technical documentation published by the Computer Center. Five major new documents are planned for NEW WYLBUR/MILTEN and an extensive users' manual describing the use of the NIH5200 CRT terminal will be published this year. A completely new comprehensive Time Sharing Guide for the DECsystem-10 has been outlined and will be completed and available to users this year. In addition, the DECsystem-10 Display Systems manual will be updated to reflect the incorporation of new displays into the OMNIGRAPH system. Technical documentation for TSO, SPOUT, CICS, COM, OCR, CPS, HASP (SHARED SPOOL), etc., as well as Job Control Language will be extensively re-written to reflect the new virtual operating environment, and an IMS Users Guide will be finalized.

All on-going activities including support activities, problem consulting, documentation distribution, and training will continue at an increased pace. The task of fine tuning the NIH Computer Utility to keep it responsive to the changing needs of the NIH, and the investigation of new computational techniques must continue so that the Utility can best support the NIH mission.

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities   1. DCRT

2. COMPUTER SYSTEMS LABORATORY   3. Alan M. Demmerle
                                           Chief

INTRODUCTION

The primary mission of the Computer Systems Laboratory (CSL) is to identify
problem areas in biomedical research and clinical care in which the computer
offers a potential for improved research productivity or improved health care.
The concentration of work is on applications where real-time data collection,
analysis, display, and experiment control are required, where economic con-
siderations favor a small computer or where equipment proximity is important.

The staff of CSL has, in addition to expertise in both the engineering and
programming aspects of laboratory computing and automation, extensive experi-
ence in working on problems in the biomedical area. Many of the laboratory's
projects require a coordinated effort between engineers and computer scien-
tists from CSL and researchers from other Divisions and Institutes.

I. COMPUTER SUPPORT FOR AUTOMATION OF LABORATORY EXPERIMENTATION

CSL is engaged in a number of projects supporting research in the physical
sciences. The primary goal of this support is automation of the collection,
processing and display of laboratory data. Achievement of this goal has,
generally, involved the design, and implementation of a number of computer
systems of varying sizes. The larger systems, usually, serve a number of
users simultaneously and require several years of effort to attain full
operational status. An example of such a system is the NIAMDD System which
serves several NIAMDD Laboratories, permitting a number of experiments
to be processed simultaneously. Smaller laboratory systems are usually
dedicated to a single user at a time, and can usually be implemented in less
time. The NMR System in NIAMDD, which is used for Fourier Transform Spectros-
copy calculation, is typical of this class of system, as is the NIAID System
which is used with experimentation concerning the structure of immunologically
important proteins.

During the past year, the CSL engineering staff has been involved in various
phases of the implementation of 10 systems aimed at automating laboratory
experiments. The capabilities of the NIAMDD System, mentioned above, have
been expanded to include processing of data from an EPR Spectrometer and
McPherson Spectrophotometer. A system for the Laboratory of Vision Research
(NEI) which was started the previous year has been made operational during
this past year. Analog voltage data relating to the photo transduction
process in the retina are collected and processed and analyzed data are
displayed. Further work has proceeded on automation of a Flourescence

Activated Cell Separator for NCI. This system was also started in the preceding fiscal year. A computer for this system has now been procured and the utility programs written to allow it to use the DCRT PDP-10 interactively for data storage and complex mathematical analysis. Interfacing to the cell sorting instrument has begun. A second system for NEI was started. This system is to be used for two different studies. The first is a study aimed at understanding the normal and pathophysiological mechanism for the control and production of eye movements. Normal volunteers as well as patients with all forms of disturbance of eye movement will be studied with mechanized visual stimulation equipment. Eye movements over a range of 0-45 degrees will be analyzed in detail. The second use involves analysis of data concerning pupil movement.

The Hybrid Computer, purchased about 10 years ago as a general utility for the NIH research community, is now being used primarily on NHLI research projects. This system and its supporting staff occupy 5 modules of Building 10. The demand for this space has become so acute that the system will be replaced with newer and more compact equipment, thereby making available 3 of the 5 modules for other purposes. Elements of the new system have been ordered and will be made operational before the old system is dismantled and removed during the coming fiscal year. The new system is to provide a comparable facility for general purpose data acquisition, A/D conversion, plotting and display.

II. CLINICAL CARE & RESEARCH

CSL has, for the last several years, become increasingly involved in the support of several clinical care and research functions at the NIH. This has occurred because of an increased understanding and awareness by clinicians of the potential of computers and automation, and also because of advances in medical instrumentation and techniques which have led to the generation of voluminous amounts of data that must be analyzed and examined prior to use in patient diagnosis and treatment.

The role of the computer in the clinical environment is still evolving. Currently, it performs functions that cannot be accomplished by manual means, provides the physician with a valuable tool in decision making and promotes direct patient care activities by relieving highly trained medical personnel of routine clerical functions. The technical requirements in this environment include the acquisition, storage, analysis and display of clinical data. For the most part, these functions are performed on-line and in real-time. All require extensive cooperation among engineers, computer scientists, programmers and medical personnel.

THE NHLI INTENSIVE CARE UNIT

This project provides for the continuous monitoring of patients in the heart surgery recovery area in order to provide the earliest possible detection of abnormal or dangerous conditions. For the past two years, the ICU System has collected and analyzed ECG, temperature, fluid loss, arterial pressure and venous pressure data from a single patient. During the past year this capability has been extended so that these same functions can be provided

simultaneously for four patients. This extension has required the optimization of the processing of the ECG and pressure wave forms. Much of the analysis of these signals is now done external to the computer using special purpose hardware developed here over the past several years. Further development of these techniques using the new microprocessor technology is now underway. These preprocessors will be used on a number of projects. An ECG preprocessor implemented with a microcomputer, for instance, will be used in the ICU System and also in conjunction with an NHLI project that requires the analysis of PVC's obtained from ambulatory patient electrocardiograms.

NUCLEAR MEDICINE DEPARTMENT

CSL has continued to contribute engineering expertise to a joint project with LAS, DCRT and the Clinical Center's Nuclear Medicine Department. We have worked toward more fully developing the potential of a computer system which has been operational for several years and an additional system which was acquired this year. The accomplishments of this project are described in the LAS report.

PHONOCARDIOGRAM RESEARCH

For the past three years, CSL has collaborated with the Surgical Branch of NHLI in the development of methods by which characteristics of the phonocardiogram can be used as diagnostic indices of prosthetic heart valve performance. We are searching for a reliable, easy to apply, non-invasive indicator. For more than one year now, phonocardiograms have been routinely taken on about six patients per week and analyzed on the hybrid computer. The analysis involves beat-to-beat correlation of heart sounds, a determination of the ratio of the amplitude of the opening sound to that of the closing sound and sound spectrographic analysis. Current indications are that the correlation technique offers no significant improvement, as a diagnostic indicator, over the opening to closing sound ratios, particularly for the SE1000 series values. Attention is now being directed to the 1200 series values, for which much less data is currently available. Partly as a result of this project, it became clear that a computerized retrieval system for the patient data collected in the Surgery Branch of NHLI was needed. The data base includes demographic data, laboratory tests, surgical notes, autopsy report data, catheterization data and phonocardiogram data on all patients. The development of this information retrieval system began this fiscal year.

CATHETERIZATION LABORATORY SYSTEM

An extensive dual goal project was started this year with the Catheterization Laboratory of NHLI. The first goal envisions on-line computer support in the acquisition and processing of data acquired during catheterization procedures. Electrocardiogram data, several blood pressures, dye concentration measurements, thermal dilution cardiac output signals, phonocardiograms, HIS bundle electrograms, and possibly other physiologic parameters are to be processed. CSL, after exploring several alternative methods of implementation recommended that an existing commercial system be procured and modified to meet specific NHLI requirements. That purchase, however, was not made this year.

The second goal of this project is to organize the medical data associated with the NIH patients who have been catheterized, into a computer-based data

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management system that can readily provide answers to complex research oriented queries. Very considerable emphasis is attached to the problem of developing techniques that will promote simple flexible data retrieval capable of being initiated and operated by the scientific user. As such techniques are perfected, it is planned to integrate them into other projects using similar data bases. An example of this projected transfer is provided by an on-going project with the Microbiology Service of the Clinical Center's Clinical Pathology Department. That Service is, among other things, (1) actively studying methods of organism identification, (2) developing resistance patterns of organisms to antibiotics, and (3) attempting to trace the existence and source of hospital infections. This effort has been greatly facilitated by a retrieval system, utilizing GNR data and antibiotic sensitivity data, that has been implemented by CSL during the past year. Although operational, however, the complexity of system use is such that CSL rather than the Microbiology Service remains responsible for operation.

III. OTHER COMPUTER SUPPORT PROJECTS

Two projects were started this year which are neither exclusively for laboratory nor clinical support. The NIEHS in the Research Triangle, North Carolina has, during the past few years, developed an increased need for computer support beyond that available to them from a keyboard terminal connected to a computer utility. Their four basic requirements are: 1) a high speed data entry facility to a remote computer utility, 2) a high speed printing and graphic output facility from a remote computer utility, 3) a capability for elementary processing of data produced by laboratory instruments such as spectrometers which produce data in a form and on a medium suitable for computer processing, and, 4) the collection, processing and retrieval of data relating to their animal colony. Analysis of these requirements led to the purchase, this year, of computer equipment capable of satisfying their first three requirements. Work has not begun on the fourth requirement. Also started this year is a computer system for the NIH Library that is designed to automate the collection and maintenance of daily transaction information (charging, discharging, reserving and reviewing library materials). The system is based on a computer to be located in the library along with optical scanning devices, a CRT terminal and other specialized input devices. Every day or so, the data collected on the library computer will be transferred to the DCRT central facility where master files will be maintained. This system is to start out as a near duplicate of one developed at the University of South Carolina and is to be further developed here in accord with NIH specific requirements.

IV. GENERAL RESEARCH

While the bulk of the work in CSL is connected with laboratory automation and clinical care, there is considerable effort devoted to other areas of computer research related to biomedical applications. Currently, there are two major areas of general research, the use of computer pattern recognition methods in biomedical problems, and the development of a medical telecommunications system.

PATTERN RECOGNITION STUDIES

Work in applying pattern recognition techniques to predict structure-activity

relationships was continued. An on-line system which attempts to predict the pharmacological activity of drugs was developed. This system, using pattern recognition and substructural analysis methodology assigns pharmacological activity in two ways. First, the methodology attempts to find overall similarity in molecules by determining how "similar" a compound is to known drugs by using the Euclidean distance criteria. Then the compound is assigned the activity of the "most similar" compound. The second procedure predetermines those substructural units that are most indicative of a pharmacological class using the learning machine. Then if a compound possesses these common substructural units, it is predicted to possess this activity. In addition, the structures of the known drugs used in assigning the activity can be displayed to check the pharmacological assignment. Thus, this empirical approach allows past biological data to guide current testing.

MEDICAL TELECOMMUNICATIONS SYSTEMS

For several years, CSL has been engaged in the development of a technology by which computer services can be made available to the medical community using only a conventional touch tone telephone as a computer terminal. The plan has been to make such services readily available so that the power of the computer can be applied in assisting physicians in such areas as diagnosis, treatment and therapy planning. A prototype system was completed more than one year ago which permits use of the push buttons on the telephone as a means of providing input to the computer, while the computer responds in voice over the telephone. Six medical application programs have been developed which are indicative of the types of applications which might be used. The medical school of the University of Wisconsin has been demonstrating this system in their hospital. Improvements to the system during the past year have been directed toward making the speech generation more economical. It is expected that a voice generator, tied to a microcomputer, will permit the use of this technology with only a modest hardware addition to any commercial time-share facility. Thus, the current need for an entire dedicated computer (SEL-810B) will be eliminated.

V. CONSULTATION

In addition to the work described above, CSL consults with researchers in need of computer expertise. This consultation can be simply providing advice on a specific problem or can result in the design of special purpose hardware or in the writing of special software. A typical example of this type of supportive work occurred with a data collection problem in NCI. Help was sought in determining the optimum method of replacing an old unreliable noisy punch paper tape system. CSL examined alternatives, specified a programmable calculator with cassette tape for the collection of long runs (24 hours) of diet intake of animal colonies, and will soon interface the new system to the instrumentation involved. Five other projects of comparable size were undertaken this year, each one consuming 3-6 man-months of effort.

CSL Summary of

LEVEL OF EFFORT AND EXPENDITURE

BY PROJECT

Project Name	Project Leader	DCRT Man-Power (M-Y/Year)		DCRT Capital Invested ($ X K) Including Maintenance		Central Facility Charges ($ X K)
		FY-74	FY-75	FY-74	FY-75	FY-75
Bldg. 2 516	Schultz	2.0	1.5	2.0	8.0	2.0
NMR	Schultz	2.0	1.5	24.8	12.0	
NIAID	Plexico	3.0	1.5	9.0	5.0	
NEI	Schultz	1.5	1.5	1.0	3.0	
NEI	Plexico		0.5			
NCI	Schultz	1.0	1.5		2.0	
ICU	Syed	7.0	5.0	80.6	90.0	11.0
Nuclear Med.	Schultz	0.5	0.5	40.0	3.0	1.0
Phonocardio-gram	Schultz	0.5	1.0	0.5		20.0
Medical Tele-communications	Plexico	1.0	1.5	14.5	17.0	
Pattern Recognition	Chu	3.0	1.0			50.0
NIEHS	Plexico		0.5			
NIH Library	Plexico		0.5		1.0	
Hybrid Replacement	Plexico		2.0		10.0	1.1
Cath Lab.	Syed		2.0			5.0
Special Consultation			3.0			
Support			3.0			
Microbiology			1.0			5.5

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities   1. DCRT

2. PHYSICAL SCIENCES LABORATORY   3. Dr. G. H. Weiss

I. OBJECTIVES

The Physical Sciences Laboratory is devoted to the study of problems in physics and chemistry that relate to the biological sciences. Several disciplines are represented in the membership of the laboratory. These include applied mathematics, theoretical chemistry, and theoretical physics. Whenever possible the theoretical studies are performed in conjunction with experimental work, either in collaboration with workers in outside units, or by members of the Physical Sciences Laboratory working in other laboratories at NIH. In addition to performing research of its own choosing, members of the Physical Sciences Laboratory provide consultation to other researchers at NIH on different topics in the disciplines represented in the Laboratory. These services are enumerated in the project reports.

II. SUMMARY OF LABORATORY PROGRAMS

1.   The Physical Sciences Laboratory together with the Fogarty Center held a symposium celebrating the fiftieth anniversary of the ultracentrifuge. Speakers from all over the world participated and proceedings of the meeting will appear, hopefully within a year. We have continued our own research on numerical solutions of the Lamm equation. These solutions have enabled us to obtain new insight into the Johnston-Ogston effect in interacting species. We have also begun a study of the wall effect in cell separation by the ultracentrifuge.

2.   Our studies in the forces important in biological phenomena have continued, and in collaboration with Professor R. P. Rand of Brock University we have succeeded in measuring the repulsive forces between membranes of the phospholipid lecithin.   This experimental arrangement allows us to further study the effects of sugars on the model membrane. A theory for the anomalous swelling pressure of the cornea has been derived. This new theory is in agreement with experimental results which show that the pressure can decrease with increasing temperature. All previous theories came to the contrary conclusion. The suggested theory can be further tested experimentally. Further work on the van der Waals forces has included the development of methods for converting absorption spectra into intermolecular forces.

3. Considerable effort has been devoted to a project on laser light scattering in biological systems. We are currently constructing an inelastic light scattering spectrometer for use at NIH to be located in Building 4. Most of the work on this apparatus has been concluded and we hope to begin actual experiments shortly. We have continued work on cellular motility and chemotaxis. In particular, we are engaging in joint experimental and theoretical studies of the cellular mechanisms of the MIF assay and in particular the use of fluctuation spectroscopy to determine mobility parameters.

4. Our work on nuclear magnetic resonance spectroscopy has focused mainly on the rapid scan technique. This allows a considerable improvement in signal to noise ratio. We have continued our studies of helix-coil transformation of polypeptides in solution, concentrating on the effects of finite chain lengths. The usual theories of this phenomenon are based on the approximation of infinite chain length. We have shown that the effects of finite chain length are important for peptide numbers up to 1,000.

5. A collaborative study with Dr. William Caveness on the long range effects of head injuries is presently being concluded. Our studies of the mortality rate and other details of death on German veterans injured in World War I has shown that severe head injuries lead to increased mortality in later life and increased deaths due to cerebrovascular causes over a control population. We have also collaborated with Dr. Eugene Fischmann of Freedmen's Hospital on the possible improvement of electrocardiographic techniques through the use of increased numbers of leads. We have so far identified the most appropriate sets of leads for new techniques of data processing of this information.

6. Our work on the use of adaptive sampling in clinical trials has consisted in the application of the likelihood methodology for treatment-control comparisons. We have shown that the likelihood selection and likelihood stopping techniques offer a considerable improvement over sequential procedures already in the literature. Another study concluded is the effects of covariant information on the performance of different adaptive sampling rules. The inclusion of covariant information is found to be mandatory for adaptive sampling.

PHS-NIH
Individual Project Report
July 1, 1974 through June 30,1975

Project Title: Theory of Biochemical Separation Technique

Previous Serial Number: 5.1

Principal Investigator: George H. Weiss, Ph.D.

Other Investigators: None

Cooperating Units: David Yphantis, Ph.D., University of Connecticut,
David Rodbard, M.D., Reproductive Research Branch,
NICHD, Thomas Pretlow, M.D., University of Alabama
Medical School, Marc Lewis, Ph.D., Laboratory for Vision
Research, NEI.

Man Years:

Total:	0.2
Professional:	0.2
Others:	0.0

Project Description:

Objectives:

To determine the physico-chemical effects influencing different
biochemical separation systems such as ultracentrifugation, chromatography,
and electrophoresis. To determine the quantitative significance of these
effects. To devise numerical techniques for processing data from chemical
separation procedures to determine properties such as molecular weight and
diffusion coefficients.

Progress in FY 1975: A symposium celebrating the fiftieth anniversary of
the ultracentrifuge was held jointly with the Fogarty Center. Proceedings
of the meeting jointly edited by G. Weiss and Marc Lewis are to be published
as a special issue of Biophysical Chemistry within a year. We have continued
our study of the resolving power of one and two dimensional separation
systems, finding that almost any criterion gives the same result for optimiz-
ing parameters provided that it takes into account the phenomenon of over-
resolution. Results of the investigation are applied to determining optimal
gel parameters in pore gradient electrophoresis. We have completed a numer-
ical and analytical study of the Johnston-Ogston effect in ultracentrifuga-
tion, finding that results previously obtained for special systems have

much wider application. We have begun a study of the wall effects in the density gradient centrifugation of cells, in collaboration with Dr. Thomas Pretlow of the University of Alabama, with the object of relating the cell loss to the initial configuration and other parameters of the experiment. We have developed a technique for extrapolating the concentration profiles in equilibrium centrifugation experiments to infinite time using an Aitken transformation. The procedure requires relatively noise-free data but has the potential of reducing experimental times by factors of at least two under almost all experimental conditions.

Keyword Descriptors: Ultracentrifuge, electrophoresis, resolution in chromotography, wall effect.

Honors and Awards: none

Publications:

Weiss, G. H., Rodbard, D.: Resolution of species showing micro-heterogeneity by zone electrophoresis and chromatographic systems. Separation Science 9, 117-124, 1974.

Weiss, G. H., Catsimpoolas, N., Rodbard, D.: Transient state iso-electric focussing: Theory. Archives of Biophysics & Biochemistry.163, 106-112, 1974.

Correia, J. J., Johnson, M. L., Weiss, G. H., Yphantis, D. A.: Numerical study of the Johnston-Ogston effect in two component systems. Biophysical Chemistry (to appear).

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Theory of the Helix-Coil Transformation of Polypeptides in
Solution

Previous Serial Number: 5.2

Principal Investigator: James A. Ferretti, Ph.D.

Other Investigators: None

Cooperating Units: Robert L. Jernigan, Ph.D., Laboratory of Theoretical
Biology, NCI

Man Years:

Total:	0.4
Professional:	0.4
Other:	0.0

Project Description:

The purpose of this project is to understand at the molecular level
the nature and underlying mechanism of the helix-random coil transition in
polypeptides. Relaxation rates for the transition have been obtained using
ultrasonic attenuation and dielectric relaxation experiments. In terms of
the theoretical model we have developed, it is possible to relate these
measured relaxation rates to the molecular rate constants and equilibrium
conformational statistics. The results are based upon a general description
of the time rate of change of the conformational probabilities in the form of
a set of coupled differential equations. We find that the effects of finite
chain length are important and that these effects can persist to greater than
1,000 peptide units.

Keyword Descriptors: Helix-coil transformation, mean relaxation rate,
conformational statistics, molecular rate constants.

Honors and Awards: None

Publications:

R. L. Jernigan and J. A. Ferretti: Mean Configurational Relaxation
Rates in Finite Length Polypeptides. J. Chem. Phys., 62, 2519-2527, 1975.

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Rapid Scan Nuclear Magnetic Resonance Spectroscopy

Previous Serial Number:

Principal Investigator: James A. Ferretti, Ph.D.

Other Investigators: None

Cooperating Units: E. D. Becker, Ph.D., Laboratory of Chemical Physics,
NIAMDD, Richard R. Ernst, Ph.D. Laboratorium fur
Physikialische Chemie, Eidgenossische Technische
Hochschule, Zurich, Switzerland, Raj K. Gupta, Institute
for Cancer Research, Philadelphia, Pa., Thomas Clem,
Biomedical Engineering Branch, DRS.

Man Years:

Total:	0.6
Professional:	0.6
Other:	0.0

Project Description:

        The technique of rapidly scanning the magnetic field or the radio
frequency to obtain NMR spectra has received further attention. The basic
method consists of rapidly scanning a response, digitizing the analog data
and storing the results in a Raytheon 704 computer. As long as the spin
system can be considered as a linear and time-independent one, the response
signals develop independently and without interference. The computer is then
used to cross correlate the response signals either with a suitable reference
response or with an appropriate analytical function. The result is an un-
distorted spectrum with considerably improved sensitivity. The principal
effort during this fiscal year has been to demonstrate the advantages of the
method and also to determine its limitations. We have demonstrated the ease
with which a portion of the spectrum of a protein in water can be scanned
without recording the HDO or H_2O peaks.   This is a distinct advantage of the
rapid scan method, since the pulse technique is severely limited due to the
dynamic range problem. We have also developed a means using rapid scan to
determine spin-lattice relaxation times.   The approach, which is in some
ways analogous to the saturation recovery method in pulse NMR is fairly
general and good for both short and long times. Together with Professor
Richard Ernst, I have investigated the effects of nonlinearity using rapid

scan on coupled spin systems. We find both experimentally and theoretically that for certain scan rates there are phase and intensity anomalies which appear when large flip angles are used to drive the spin system into a non-linear region.

Keyword Descriptors: Rapid scan, cross correlation, Nonlinear response

Honors and Awards: None

Publications:

Gupta, Raj K., Ferretti, James A., and Becker, Edwin D.: Spin-Lattice Relaxation Measurements Using Rapid Scan FT NMR. J. Magnetic Resonance, 16, 505-507, 1974.

Project Title: Cellular Motility and Chemotaxis

Previous Serial Number: 5.4

Principal Investigator: Ralph Nossal, Ph.D.

Other Investigators: George H. Weiss, Ph.D.

Cooperating Units: Leonard D. Kohn, M.D., Yao T. Chang, M.D., Laboratory of
                    Biochemical Pharmacology, NIAMDD.

Man Years:

            Total: 0.8
            Professional: 0.6
            Other: 0.2

Project Description:

        Primary among the objectives of this project is the elucidation of
cellular mechanisms involved in chemoreception and cellular response, parti-
cularly regarding cell motility. Theories are constructed to related macro-
scopic mobility coefficients to microscopic response parameters and experi-
ments are performed with both bacterial (E. Coli) and mammalian cells
(leukocytes). New assay systems, involving laser light scattering and time-
lapse cinemicrography are employed, and procedures are devised to isolate
materials from cell surfaces for assay on reconstituted lipid bilayers.

        One aspect of these studies relates to leukocyte migration as an
assay for cellular immune sensitivity (MIF assay). In collaboration with Dr.
L. D. Kohn of LBP/NIAMDD, we have modified migration inhibition assays and
applied them to study autoimmunity in patients suffering from exophthalmic
Graves' disease. A mathematical theory for the capillary MIF assay has been
developed, with a view towards optimizing assay design.

        The cellular mechanisms of the MIF assay are being investigated by
cinemicrographic techniques which rely upon novel occupation number schemes
for determining mobility parameters (in collaboration with Y. T. Chang, LPB/
NIAMDD).

Cellular chemotaxis is implicated in inflammation and wound healing, and in the recognition of bacteria by leukocytes. It also may be related to tissue organization in multicellular organisms.

Keyword Descriptors: Chemotaxis, migration inhibition, cellular immunity, cell locomotion.

Honors and Awards: None

Publications:

Nossal, R., and Weiss, G. H.: A generalized Pearson random walk allowing for bias. J. Stat. Phys. 10, 245-253, 1974.

Nossal, R. and Weiss, G. H.: A descriptive theory of cell migration on surfaces. J. Theor. Biol. 47, 103-113, 1974.

Project Title: Measurement of van der Waals Forces

Principal Investigators: V. A. Parsegian, Ph.D., G. H. Weiss, Ph. D. and
                          James E. Kiefer

Other Investigators: None

Cooperating Units: Arnold Shih, Ph.D., National Bureau of Standards, and
                    Malcolm Shrader, Ph.D., Naval Weapons Research Laboratory.

Man Years:

          Total: 0.8
          Professional: 0.6
          Other: 0.2

Project Description:

        To continue to develop the theory and measurement of van der Waals electrodynamic forces to be useful in the study of biological organization.

        Formulations of van der Waals forces have been extended to apply to the attraction of atoms or molecules with solid walls and to the attraction between curved parallel surfaces. We have continued to progress in developing methods for converting absorption spectra (from Oak Ridge National Laboratory) into intermolecular forces.

        Measurements of forces attracting atoms or molecules in a beam to a planar surface have been carried out (at the National Bureau of Standards). Comparison with theoretical expressions developed in this lab are much better than theories previously available.

        Wetting by water of clean surfaces seems to be compatible with our present understanding of van der Waals forces. We have collaborated success-fully with Dr. Malcolm Schrader in making measurements of water adhesion. These measurements, contrary to earlier findings and earlier theories, suggest that conducting surfaces are a uniquely good surface for the ad-hesion of polar materials.

There are several parallels between the adhesion of cells to material substrates and that of liquids to solid bodies. The ability to analyze precise wetting experiments will strengthen our ability to look at cellular adhesion.

The measurement between beam particles and substrate are not directly biological. They are crucial to rigorous tests of the theoretical physical methods that we are using in a biological context where their accuracy cannot be verified very well.

Keyword Descriptors: van der Waals forces, theory; van der Waals, measurement; molecular beams, wetting of surfaces.

Publications:

Parsegian, V. A.: Formula for the electrodynamic interaction of point particles with a substrate. Molec. Phys. 27, 1503-1511, 1974.

Parsegian, V. A. and Weiss, G. H.: Electrodynamic interactions between curved parallel surfaces. J. Chem. Phys. 60, 5080-5085, 1974.

Shih, A. and Parsegian, V. A.: Van der Waals forces between heavy alkali atoms and gold surfaces: Comparison of measured and predicted values. Physical Review A (to appear).

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Physical Force Interactions Between Cell Membranes and
                  Cell Membrane Analogues

Principal Investigator: V. A. Parsegian, Ph.D.

Other Investigators: None

Cooperating Units: D. Gingell, Ph.D., Middlesex Hospital Medical School,
                      London, R. P. Rand, Ph. D., and D. M. LeNeveu, Ph.D.,
                      Brock University, St. Catherine's, Ontario.

Man Years:

        Total: 0.4
        Professional: 0.4
        Other: 0.0

Project Description:

        To measure, compute, and learn to modify forces between cell
membranes.

        We have succeeded in measuring the repulsion forces between membranes
of the phospholipid lecithin.   This has been possible by exerting an osmotic
stress on a stack of membranes while doing x-ray diffraction to measure their
spacing.   Repulsion forces are mechanically large between these membranes
and exceed two atmospheres even at 20 Angstrom separation.   With the success
of this method we are now introducing selected lipids bearing charge or
sugars into the model membranes to measure systemic changes in membrane
repulsion forces.

        We have found that small sugar solutes in the medium between model
membranes apparently modify the van der Waals attraction forces which create
the lamellar array.   This effect of solvent has been predicted by the general
theory of forces but not been seen before.

        Dr. D. Gingell has done two experiments that are a direct outgrowth
of his work here in the DCRT.   First, he has found red cell aggregation
following precisely that predicted by modulating electric charge on the
membrane surface.   (His data were processed here at the DCRT during his visit
last summer.)   Second, he has succeeded in designing a substrate to which

cells may adhere which is at the same time an electrode to which attractive or repulsive potentials may be applied. He has demonstrated stable attraction of cell-to-substrate with an apparent gap between them. Modulation of the applied potential and observation of resultant cellular sticking or non-sticking will allow us to make quantitative estimates of cellular attraction forces.

We expect that the above measurements coupled with force computations will continue to give us a coherent physical understanding of cellular association in tissues. There is good evidence that aberrations in the electrostatic repulsion between cells are what create a failure to form good tissues.

Repulsion between membranes also affects cell fusion and vesicle fusion. Accurate measurements will be helpful in determining fusion mechanisms.

Keyword Descriptors: Cell membrane interaction, measurement, computation, electrostatic forces, electrodynamic forces.

Honors and Awards: None

Publications:

Parsegian, V. A. : Possible modulation of reactions on the cell surface by changes in electrostatic potential that accompany cell contact. Ann. N. Y. Acad. Sci. 238, 362-371, 1975.

Parsegian, V. A.: A physical approach to the study of cell membranes. Twelve Lectures to be published in the book based on the Simon Fraser University Summer School on Membranes, ed. K. Colbow, Alta Lake, B.C. Canada.

Project Title: Influence of Electric Forces on the Organization of Proteins
and Model Systems

Principal Investigators: V. A. Parsegian, Ph.D., Stephen L. Brenner, Ph.D.,
and R. J. Nossal, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years:

        Total: 1.5
        Professional: 1.5
        Other: 0.0

Project Description:

        To learn how interactions between electrically charged bodies,
particularly proteins, govern their mutual arrangement and perturb their
surroundings.

        We have developed an efficient way to formulate the electrostatic
forces between charged particles in salt solution.   This method has been
applied to rod-like particles such as the Tobacco Mosaic virus and to
spherical bodies.

        We have derived a suggestion for the "anomalous" swelling pressure
of the cornea. This pressure is seen to go down with increasing temperature
while all previous theories predicted the reverse.   Our suggestion includes
direct measurements to test its validity.

        The transparency of the cornea is highly sensitive to the amount of
water it holds. Apparently a major force for its swelling to opacity is the
electrostatic repulsion between its protein components. By learning to probe
and possibly to modify the pressure for swelling we may have a better under-
standing for preventing unwanted swelling.

        We have also applied the theory of attractive (electrodynamic) and
repulsive (electrostatic) forces to the formation of ordered arrays of
Tobacco Mosaic virus particles. Different causes suggest different relations
between interval separation and medium salt concentration.

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Keyword Descriptors: Electrostatic forces, corneal swelling, Tobacco Mosaic
          virus.

Honors and Awards: None

Publications:

        Brenner, S. L. and Parsegian, V. A.: A physical method for
deriving the electrostatic interaction between rod-like polyions at all
mutual angles. Biophys. J. 14, 327-334, 1974.

        Brenner, S. L. and Parsegian, V. A.: Suggested explanation for the
anomalous temperature dependence of the corneal swelling pressure. Exptl.
Eye Research (to appear).

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Correlation Function Spectroscopy/Laser Light Scattering

Previous Serial Number: 5.6

Principal Investigator: Ralph Nossal, Ph.D.

Other Investigators: Stephen L. Brenner, Ph.D.

Cooperating Units: L. Kohn, M. D. Laboratory of Biochemical Pharmacology,
                   MIAMDD, B. Berne, Columbia University, S.H. Chen,
                   Massachusetts Institute of Technology

Man Years:

              Total: 0.6
              Professional: 0.6
              Other: 0.0

Project Description:

        A principal objective of this project is to develop laser inelastic
light scattering techniques for performing measurements on biological cells
and macromolecules. Theoretical analyses are performed in conjunction with
various experimental studies: major emphasis is related towards problems of
biological transport and cellular motility.

        Previously, experimental work was performed in laboratories located
at the Massachusetts Institute of Technology and Columbia University. How-
ever, we currently are constructing an inelastic light scattering spectro-
meter for use at NIH, to be located in facilities being made available to us
by the Laboratory of Biophysical Chemistry, NIAMDD. The next phases of
instrument development will involve design and construction of apparatus for
detecting electrophoretic mobilities and also, instrumentation for performing
fluorescence intensity fluctuation spectroscopy.

        Laser inelastic light scattering techniques enable rapid and
precise measurements of various physical parameters pertaining to biological
molecules and cells. In principle, any process giving rise to refractive
index fluctuations can be monitored; for example, concentration fluctuations
can be used to determine diffusion coefficients of macromolecules, rate
constants of bimolecular reactions, or swimming speed distributions of motile
microorganisms.

Numerous applications structures larger than the wavelength of light can be envisioned. However, in this case new theories to relate observed spectra to underlying dielectric constant fluctuations must be provided. Thus, in the past year we have elucidated the effects of cell substructures on measurements of mobility coefficients, and also have provided a rubric for interpreting diffusion coefficient data for large anisotropic particles.

Keyword Descriptors: Lasers, light scattering, macromolecules, diffusion coefficients, motility, correlation functions.

Publications:

Boon, J.P., Nossal, R., and Chen, S.H.: Light scattering spectrum due to wiggling motions of bacteria. Biophys. J. 14: 847-864, 1974.

Berne, B., and Nossal, R.: Inelastic light scattering by large structured particles. Biophys. J. 14: 865-880, 1974.

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Consulting Services

Previous Serial Number: 5.8

Principal Investigator: George H. Weiss, Ph.D.

Other Investigators: Mildred L. McNeel

Cooperating Units: William F. Caveness, M.D., Laboratory of Experimental
Neurology, NINDS, Eugene J. Fischmann, M.D., Freedmen's
Hospital, Jay Herson, Ph.D., Howard University, Steven
Weinstein, Ph.D., Howard University, Charles W. Boone,
M.D., Viral Biology Branch, NCI, Steven Yeandle, Ph.D.,
Naval Medical Center.

Man Years:
Total: 1.6
Professional: 1.0
Other: 0.6

Project Description:

Members of the Physical Sciences Laboratory render assistance to
other, primarily experimental scientists, in the areas of mathematics,
statistics, theoretical physics and chemistry.

Progress in FY 1975:   We have nearly completed a study of the effects of
head injury on mortality in German veterans of World War I.   The mortality
rate and causes of death were correlated with severity of injury for varying
numbers of head injured and uninjured controls from the same military units.
The data indicate increasing mortality with increasing severity of injuries
of different kinds, with an increase in the fraction of deaths due to cerebro-
vascular causes in the head injured.   This work will shortly be written up
and submitted for publication.

Considerable effort was made in assisting investigators at Freed-
men's Hospital to determine the effectiveness of potential mapping in improv-
ing the performance of standard electrocardiography.   For this purpose it was
necessary to determine the best diagnostic variables from multilead data. So
far we have considered only the QRS complex, and compared the time variation

of electrode potentials from different leads and at different times. Some tentative identifications of the most informative leads have been made using pattern recognition techniques. We have also examined the problem by means of discriminant analysis but this has proved to be less useful. Some techniques from signal processing appear to have some promise in this type of problem. More data is awaited to complete this study.

With Dr. C. W. Boone we have begun to develop some models to interpret experiments related to contact inhibition.

We have also developed mathematical theory to test different hypotheses about secondary reactions to visual stimuli in the eye, which have been studied experimentally by Dr. Steven Yeandle. We have found that several hypotheses are indistinguishable when the fraction of primary events that give rise to secondary responses are small.

Keyword Descriptors: Head injuries, mortality rates, cerebrovascular accidents, potential mapping in electrocardiography, pattern recognition.

Honors and Awards: None

Publications:

Weiss, G. H. and Yeandle, S.: Distribution of response times in visual sense cells after weak stimuli. J. Theoret. Biol. (to appear).

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Miscellaneous Studies

Previous Serial Number: 5.9

Principal Investigators: George H. Weiss, Ph.D.

Other Investigators: James E. Kiefer

Cooperating Units: David G. Hoel, Ph.D., Biometry Branch, NIEHS, Menachem
Dishon, Ph.D., Weizmann Institute of Science, Rehovot,
Israel, Richard Simon, Division of Cancer Treatment, NCI,
Dennis Blumenfeld, Ph.D., University of London, Donald
R. McNeil, Ph.D., Princeton University, Robert J. Rubin,
Ph.D., National Bureau of Standards.

Man Years:

Total: 0.8
Professional: 0.4
Others: 0.4

Project Description:

We have continued work on adaptive sampling in clinical trials,
with the object of reducing either the expected number of patients in a
clinical trial, the expected number of patients administered the poorer
treatment during the course of a clinical trial, or the number of failures
during the trial.   Specifically, further applications of likelihood techni-
ques for the stopping rules of sequential trials, as well as for adaptive
sampling were made to the problem of choosing the better of a treatment
compared to a control, where the new treatment can be as good as, or better
than, the control.   The likelihood sequential design was found to be the
best of competing trial designs.   Another topic that was investigated was
the design of a clinical trial in which the maximum number of failures during
the trial is fixed.   Here we have showed that for many values of the
probability of success, alternating allocation of patients to treatments is
preferred to adaptive allocation, as suggested by Fushimi.   Another topic
investigated was the effect of minimizing the expected number of failures
during the course of a clinical trial rather than the expected number of
patients given the poorer treatment.   Here it was found that this design
criterion tended to favor alternating allocation as opposed to adaptive
allocation in trial design.   Finally we have investigated the effects

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of covariates on clinical trial design, and found that they have a crucial importance when a trial is designed, and may altogether vitiate the use of adaptive allocation.

The extension of a singular perturbation technique developed for studying chromatographic systems, has been made to the solution of certain Fokker-Planck equations especially relevant to noise in lasers.

Together with Dr. R. J. Rubin we have developed the theory of ordered spans of random walks with relation to the configurations of polymer chains. Recent interest in such problems has been stimulated by the work of Stockmayer and Solč on the asymmetry of random walk models for polymer chains even when the step probabilities are isotropic. The ordered spans give another measure of this asymmetry which can persist to very large chain sizes.

We have continued a study of acoustic pollution from traffic by enumerating the effects of non-exponentially distributed headway spacings. These are shown to be of considerable importance in decreasing noise variance, which has been shown to be a critical factor in environmental impact.

Together with Professor D. R. McNeil we have developed a technique for estimating parameters in birth and death processes in large populations. These processes occur frequently in ecological and epidemiological models, and the technique that we have developed is expected to have wide application.

Keyword Descriptors: Clinical trials, adaptive sampling, sequential analysis, likelihood stopping, random walks, ordered spans, Fokker-Planck equations, singular perturbation, birth and death processes, estimation techniques.

Honors and Awards: None

Publications:

Hoel, D. G., Sobel, M., Weiss, G. H.: Comparison of methods for choosing the best binomial population with delayed observations. J. Stat. Comp. and Simul. (to appear).

Hoel, D. G., Sobel, M., Weiss, G. H.: A survey of adaptive sampling for clinical trials, in Advances in Biometry (to appear).

Kiefer, J. E., Weiss, G. H.: Truncated version of a play-the-winner rule for choosing the better of two binomial populations. J. Am. Stat. Assoc. 69, 807-809, 1974.

Simon, R., Weiss, G. H.: A class of adaptive sampling schemes for selecting the better of two binomial populations. J. Stat. Comp. and Simul. (to appear).

Hoel, D. G., Weiss, G. H.: A clinical trial design with a fixed maximum number of failures. Commun. in Stat. (to appear).

Hoel, D. G., Simon, R., Weiss, G. H.: Reexamination of the problem of choosing the better of two treatments in the context of clinical trials. Proc. Nat. Acad. Sci. (to appear).

Weiss, G. H., Dishon, M.: Application of a singular perturbation expansion to the solution of certain Fokker-Planck equations. J. Statist. Phys. (to appear).

Blumenfeld, D. E., Weiss, G. H.: Some radial and direction dependent models for densities of homes and workplaces. Transp. Res. 8, 149-155, 1974.

Blumenfeld, D. E., Shrager, R. I., Weiss, G. H.: Spatial distributions of homes for journeys to work by different modes of transport. Transp. Res. 9, 19-23. 1975.

Blumenfeld, D. E., Weiss, G. H.: Attenuation effects in the propagation of traffic noise. Transp. Res. (to appear).

Blumenfeld, D. E., Weiss, G. H.: Effects of headway distributions on second order properties of traffic noise. J. Sound and Vib. (to appear).

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities	1. DCRT
2. LABORATORY OF APPLIED STUDIES	3. Eugene K. Harris
	Chief

During the past year, the Laboratory of Applied Studies (LAS) has strengthened those collaborative ties within NIH and extramurally which enable application of the mathematical and computing science methods developed by LAS staff.

For example, expertise in the numerical solution of partial differential equations under unusual boundary conditions was applied to the measurement of wall shear stress in model arteries as part of a cooperative study with NHLI and DRS (BEIB) scientists engaged in research on the development of atherosclerotic lesions at arterial branch points (Project No. 3.4). Similarly, continuing close collaboration among LAS, Nuclear Medicine and I/D clinical staff, particularly in NHLI, have produced several new applications of computer-based radionuclide scintigraphy with benefits to patient care and evaluation (Project No. 3.2). Two of these techniques, allowing high-resolution but non-invasive studies of dynamic changes in ventricular volume and myocardial contractility throughout the average cardiac cycle, have become important adjuncts to cardiac catheterization in patients with coronary artery disease and valvular diseases.

Another example is represented by the special skills in computer graphics which laboratory staff have applied to various projects in cooperation with NIH investigators. A noteworthy product of this work is the integrated plotting package, not initially developed at NIH but substantially improved here and modified for running on the NIH central computing system. One feature of this series of programs provides contour mapping of bivariate frequency distributions, particularly useful for epidemiologic investigations (e.g., Reference 13).

Finally, in other areas, such as the evaluation of computerized systems for interpretation of electrocardiograms (Project No. 3.1); the development of realistic models of transport of substrate through the microcirculation (Project No. 3.4); or the statistical analysis of serial blood chemistry studies in normal volunteers and patients (Project No. 3.6), the Laboratory has strengthened its collaboration with individuals and organizations outside the NIH actively working in these areas. For example, LAS staff members are currently serving as advisors to governmental agencies in this country and abroad on problems concerning the selection of ECG analysis programs and the data processing of time series of biochemical profiles in normal subjects.

As in past years, LAS staff participated in NIH educational programs. Dr. J. E. Fletcher, Head of the Applied Mathematics Section, is the current chairman of the FAES Department of Mathematics where he teaches many of the advanced applied mathematics courses. The course taught in FY 75 was Methods of Mathematical Physics I and II. Mr. J. D. Ashbrook conducts a regular course in computer graphics as part of the DCRT in hours training course program.

In July 1974 the Biomathematics and Statistics Section was detached from LAS to provide the leadership required for a new laboratory within DCRT (LSMM). Dr. James E. Mosimann, formerly head of this section, was designated chief of the new laboratory.

LAS reports published or "in press" during FY 75:

1. Agress, H., Jr., Levenson, S.M., Gelfand, M.J., Green, M.V., Bailey, J.J. and Johnston, G.S.: Application of computer-generated functional (parametric) maps in radionuclide renography. Proceedings of the Fifth Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. U.S. Atomic Energy Commission Technical Information Center, Oakridge, Tennessee, 1975 (in press).

2. Ashbrook, J.D., Spector, A.A., Santos, E.C., and Fletcher, J.E.: Long chain fatty acid binding to human plasma albumin. Journal of Biological Chemistry, Vol. 250, No. 6, pp. 2333-2338, March 1975.

3. Ashbrook, J.D., and Sande, G.: A User's Guide to the Integrated Plotting Package. U.S. DHEW, PHS, NIH, DCRT, LAS., Wash., D.C., U.S. Govt. Print. Off., 1975, 120 pp.

4. Bailey, J.J., Itscoitz, S.B., Hirshfeld, J.W., Jr., Grauer, L.E., and Horton, M.R.: A method for evaluating computer programs for electrocardiographic interpretation. I. Application to the experimental IBM program of 1971. Circulation 50: 73, 1974.*

5. Bailey, J.J., Itscoitz, S.B., Grauer, L.E., Hirshfeld, J.W., Jr., and Horton, M.R.: A method for evaluating computer programs for electrocardiographic interpretation. II. Application to version D of the PHS program and the Mayo Clinic program of 1968. Circulation 50: 80, 1974.*

6. Bailey, J.J., Horton, M.R., and Itscoitz, S.B.: A method for evaluating computer programs for electrocardiographic interpretation. III. Reproducibility and the sources of program errors. Circulation 50: 88, 1974.

7. Fletcher, J.E.: A Model Describing the Unsteady Transport of Substrate to Tissue from the Microcirculation. SIAM J. Applied Math., Vol. 29, No. 2, September 1975 (in press).

8. Fletcher, J.E.: Distributed Parameter Modeling of the Microcirculation. Systems Analysis of Biomedical Transport, edited by D.D. Reneau, Marcel Dekker, Inc., New York (in press).

9. Green, M.V., Agress, J., Jr., Brody, W.R., Pearlman, A.S., Itscoitz, S.B., and Johnston, G.S.: A comparison of high temporal resolution left ventricular volume curves before and after initial replacement. Proceedings of the Fifth Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. U.S. Atomic Energy Commission Technical Information Center, Oak Ridge, Tennessee, 1975 (in press).

10. Green, M.V., Ostrow, H.G., Douglas, M.A., Myers, R.W., Bailey, J.J., and Johnston, G.S.: Scintigraphic cineangiography of the heart. Medinfo 1974, North Holland Publishing Company, Amsterdam, August 1974, pp. 827-830.

11. Green, M.V., Ostrow, H.G., Douglas, M.A., Myers, R.W., Scott, R.N., Bailey, J.J., and Johnston, G.S.: High temporal resolution ECG-gated scintigraphic angiocardiography. J. Nucl. Med. 16: 95, 1975

12. Harris, E.K.: Effects of intra- and interindividual variation on the appropriate use of normal ranges. Clin. Chem. 20: 1535, December 1974.

13. Hoffman, H.J., Stark, C.R., Lundin, F.E., Jr., and Ashbrook, J.D.: Analysis of birthweight, gestational age, and fetal viability, U.S. births, 1968. Obstetrical and Gynecological Survey, Vol. 29, No. 9, pp. 651-681, September 1974.

14. Horton, M.R., and Bailey, J.J.: Computer assisted electrocardiographic interpretation: I. Evaluation of computer processing. In Jenkin, M.A. (ed): Clinical Medicine and the Computer - Proceedings of the Fourth Annual Conference of the Society for Computer Medicine. Minneapolis, Minnesota, Society for Computer Medicine, Section 2.6, pp. 1-5, 1974.

15. Lutz, R.J., Cannon, J.N., Fletcher, J.E., and Fry, D.L.: The Measurement of Wall Shear Stress in Model Arteries by an Electrochemical Technique. Proceedings of ACEMB, October 1974.

16. Pottala, E.W. and Mortimer, J.A.: A hybrid compartmental model for the alligator purkinje cell. 1: Preferred somatopetal conduction of dendritic spikes and soma-axon interaction. J. Neurosci. Res. 1975 (in press).

17. Rinzel, J., and Rall, W.: Transient response in a dendritic neuron model for current injected at one branch. Biophys. J. 34, 1974.

18. Rinzel, J.: Voltage transients in neuronal dendritic trees. Federation Proc. 34: 1350-1356, 1975.

19. Rinzel, J: Spatial stability of traveling wave solutions of a nerve conduction equation. Biophys. J., 1975 (in press).

20. Simpson, R.B., Ashbrook, J.D., Santos, E.C., and Spector, A.A.: Partition of fatty acids, Journal of Lipid Research, Vol. 15, pp. 415-422, July 1974*.
   *Reported in FY 74 as "in press".

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Evaluation of Computer Systems for ECG Analysis

Previous Serial Number: 3.2

Principal Investigator: J. J. Bailey

Other Investigators: M. R. Horton, S. B. Itscoitz

Cooperating Units: Cardiology Branch, NHLI; ECG Laboratory, CC

Man Years:

     Total: 1.3
     Professional: 1.2
     Others: 0.1

Project Description:

     Objective:

          To assess on a sound statistical and clinical basis, the
          usefulness of computer systems for ECG analysis.

     Progress during FY 75:

          This work begun in FY 70 has involved the study of various methods
          for ECG analysis, including the use of orthogonal transforms
          (Fourier, Hambly), use of vector loops, and use of computer
          programs to interpret resting ECGs. In FY 74 a clinical evalua-
          tion of three such programs was completed (publications 1-3).

          In FY 75 an updated (improved) version of the IBM program was
          implemented and is now in daily use for routine ECGs from the
          Clinical Center. A 360 version of AVA 3.4 (Pipberger) program
          which uses Frank lead data was implemented and has been distributed
          to users in Europe and elsewhere in the U. S. Reproducibility of
          the AVA 3.4 program was tested by the previously reported method
          (publ. 3 & 4) and the results submitted for publication. A
          reliable method for acquiring ECG data on clinically documented
          cases from the Royal Glasgow Infirmary, Scotland has been achieved.

Proposed Course:

NHLI now has the capacity to provide good clinical documentation of cases through the use of cardiac catheter studies, echocardiography, radionuclide angio-cardiography, and myocardial scintigraphy. These cases will make excellent material with which the heuristic algorithms for the ECG diagnosis of chamber enlargement/overload in the IBM program can be tested and likewise also the multivariate statistical algorithms of the AVA 3.4 program. It is also proposed to compare the IBM program against the McFee lead program developed by the Royal Glasgow Infirmary using their clinically documented cases.

Keywords:

ECG analysis, heart disease, computer programs, clinical applications, clinical evaluations.

Publications:

1. Bailey, J.J., Itscoitz, S.B., Hirshfeld, J. W., Jr., Grauer, L.E., Horton, M.R.: A method for evaluating computer programs for electrocardiographic interpretation. I. Application to the experimental IBM program of 1971. Circulation 50: 73, 1974.*

2. Bailey, J.J., Itscoitz, S.B., Grauer, L.E., Hirshfeld, J.W.,Jr., Horton, M.R.: A method for evaluating computer programs for electrocardiographic interpretation. II. Application to version D of the PHS program and the Mayo Clinic program of 1968. Circulation 50: 80, 1974.*

3. Bailey, J.J., Horton, M.R., Itscoitz, S.B.: A method for evaluating computer programs for electrocardiographic interpretation. III. Reproducibility and the sources of program errors. Circulation 50: 88, 1974.*

4. Horton, M.R., and Bailey, J.J.: Computer assisted electrocardiographic interpretation: I. Evaluation of computer processing. In Jenkin, M.A. (ed): Clinical Medicine and the Computer - Proceedings of the Fourth Annual Conference of the Society for Computer Medicine. Minneapolis, Minnesota., Society for Computer Medicine, Section 2.6, pp. 1-5, 1974.

*Reported in FY 74 as "in press".

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Computer Systems for Nuclear Medicine

Previous Serial Number: 3.2

Principal Investigators: J. J. Bailey, M. V. Green (NM/CC)

Other Investigators: H. Agress, Jr., M. A. Douglas,
                      H. G. Ostrow, S. L. Bacharach,
                      S. M. Levenson, B. R. Line, G. S. Johnston,
                      W. R. Brody, D. R. Redwood, S. B. Itscoitz

Cooperating Units: Nuclear Medicine Department, Clinical Center, NIH
                    Cardiology Branch, NHLI
                    Pulmonary Branch, NHLI
                    Surgical Neurology Branch, NINDS
                    Computer Systems Laboratory, DCRT

Man Years:

    Total: 2.7
    Professional: 2.6
    Others: 0.1

Project Description:

    Objectives:

        To provide computer-based mathematical analysis in support of
        diagnostic activities in the Nuclear Medicine Department (NM)
        of the Clinical Center.

    Progress during FY 75:

        Since FY 72 LAS with support from CSL and in collaboration with
        the NM has accomplished the specification, selection, and acquisi-
        tion of a minicomputer system which was mated to two gamma
        scintillation cameras in NM. Subsequently LAS programmers have
        developed and implemented extensive software (on both the NM
        minicomputer system and the PDP-10 facility in DCRT) which has
        found wide-ranging applications, including time function manipu-
        lation, curve fitting, and functional mapping for dynamic studies;
        orthogonal transforms for image restoration by deconvolution and
        for non-restorative image enhancements; and interpolation, expan-
        sion, and contraction of image arrays.

The most important clinical application developed in FY 74 and FY 75 is the computer-based ECG-gated technique of radionuclide angiocardiography (publications 1, 2, and 4). Because of its non-invasive, non-surgical nature (cf. cardiac catheterization) requiring no anesthesia and less radiation dose than a single chest Xray, this study can be repeated frequently or can be performed on patients too sick to undergo cardiac catheterization. Thus, this technique shows considerable promise as an addition to the diagnostic armamentarium of clinical cardiology.

Another important computer-based technique begun in FY 75 is ECG-gated myocardial scintigraphy during rest and stress using radio-nuclide labeled macroaggregated human serum albumin or albumin microspheres. This technique promises to help determine the pathophysiologic effect of anatomic lesions revealed by coronary angiography and thereby add considerably to the evaluation of patients who might be candidates for coronary artery surgery.

A third computer-based method involving functional (parametric) maps in radionuclide renography was begun in FY 73. In FY 74 and FY 75 this method was applied to 130 patients and was found to enhance the detection of functional abnormalities in more than one-third of the cases (publication 3).

The computer-based method for ventilation and perfusion scanning of the lungs was begun in FY 73. At that time it proved useful in following the changes in pulmonary dynamics in patients who underwent surgical repair of valvular heart disease. In FY 74 and FY 75 this method is being refined by the incorporation of volume gating.

During FY 75 the use of computer-based statistical studies of "flooded" gamma camera fields revealed non-uniformities in the camera response which, heretofore, had been unsuspected. The photomultipliers of the camera were re-tuned and this method is now being used weekly as a quality control measure for the gamma camera data.

In FY 75 computer-based methods for determining regional blood flow are being used to study the course of experimental cerebral infarction in monkeys.

Proposed Course:

The method for radionuclide angiocardiography will be validated using patient data from cardiac catheter laboratory and also experimental data in baboons with a surgically emplaced flowmeter about the ascending aorta. This method will also be used to detect regional abnormalities in left ventricular wall motion in patients with coronary heart disease. The method for myocardial scintigraphy will be used to assess coronary artery disease in

NHLI patients. The functional mapping of radionuclide renography will be added to the nuclear medicine armamentarium as a standard procedure. The method for ventilation/perfusion scanning of the lung will be used to study NHLI patients with a variety of pulmonary abnormalities and also patients from the D.C. Veterans Administration Hospital who have interstitial pulmonary fibrosis. Work on image enhancement through use of orthogonal transforms and other techniques and methods of pattern recognition in nuclear medicine will be extended.

Keywords:

radionuclide, radioisotope, nuclear medicine, scanning, scinti-photography, non-invasive techniques, computer analysis, coronary heart disease, myocardial infarct, left ventricular wall motion, ejection fraction, renography, renal function, functional mapping, pulmonary function, ventilation/perfusion, pulmonary disease, stroke, cerebral blood flow, iodohippuran-I 131, xenon-133, xenon-127, technecium-99m.

Publications:

1. Green, M.V., Ostrow, H.G., Douglas, M.A., Myers, R.W., Bailey, J.J., and Johnston, G.S.: Scintigraphic cineangiography of the heart. Medinfo 1974, North Holland Publishing Company, Amsterdam, August 1974, pp. 827-830.

2. Green, M.V., Ostrow, H.G., Douglas, M.A., Myers, R.W., Scott, R.N., Bailey, J.J., and Johnston, G.S.: High temporal resolution ECG-gated scintigraphic angiocardiography. J. Nucl. Med. 16: 95, 1975.

3. Agress, H., Jr., Levenson, S.M., Gelfand, M.J., Green, M.V., Bailey, J.J., and Johnston, G.S.: Application of computer-generated functional (parametric) maps in radionuclide renography. Proceedings of the Fifth Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. U.S. Atomic Energy Commission Technical Information Center, Oak Ridge, Tennessee, 1975 (in press).

4. Green, M.V., Agress, J., Jr., Brody, W.R., Pearlman, A.S., Itscoitz, S.B., and Johnston, G.S.: A comparison of high temporal resolution left ventricular volume curves before and after initial replacement. Proceedings of the Fifth Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. U.S. Atomic Energy Commission Technical Information Center, Oak Ridge, Tennessee, 1975 (in press).

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Investigations of Physiologic Signals and
                 Simulation Models by Distributed Hybrid
                 Computing

Previous Serial Number: 3.6

Principal Investigators: Erik Pottala

Other Investigators: J. J. Bailey, J. B. Eisenberg, G. Wright,
                       D. Humphrey, J. Mortimer

Cooperating Units: National Institute of Occupational
                       Safety and Health; Emory University,
                       Atlanta, Georgia; University of Minnesota,
                       Minneapolis, Minnesota

Man Years:

    Total: 1.9
    Professional: 1.8
    Others: 0.1

Project Description:

    Objectives:

        (1) To develop physiologic simulation models using
             distributed hybrid computing implemented on the
             LAS laboratory mini-computer with special pur-
             pose microprocessors:

            (a) in neurophysiology to simulate neural
                 networks and central nervous subsystems
                 (e.g. cerebellum),

            (b) in cardiovascular physiology to develop
                 a global model of circulatory dynamics
                 which can be easily modified to simulate
                 pathophysiologic states (e.g. valvular
                 disease).

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(2) To develop the LAS mini-computer system as
     a research tool for handling physiologic data.

Progress during FY 75:

Neural network simulation employing physiologically
realistic hardware neural models, which incorporate
a distributed input system (analogous to a dendritic
net) with simulated action potentials, has been
pursued since FY 72. In FY 74 a neural hardware
model interfaced with the mini-computer system was
used to study a small neural net and show how an
action potential can modify the shape and duration
of post-synaptic potentials and their spatio-temporal
interactions. This work with small neural nets and
their reciprocal inhibition-excitation behavior has
been extended to the study of the cerebellum (publ. 1).

Development of the LAS mini-computer system has
continued. It has been interfaced with the Marquette
tape drive (for routine ECGs from the Clinical
Center); with the Honeywell 7600 analog tape trans-
port; with a general purpose switch-filter network;
with a real time spectral analyzer and ensemble
averager; and with the neural control panel for the
model work described above.

This system is capable of processing various analog
(physiologic) signals. For example, in FY 74 and
75, electromyographic signals collected at the
National Institute of Occupational Safety and Health
from stressed subjects were analyzed by this system
using the spectrum analyzer. The optimum ranges of
power spectra for this study were determined by this
analysis and the results are now being used to study
muscle fatigue. Another example involves ECG data
collected at the Royal Glasgow Infirmary (see 3.2).
These data contain varying levels of 50 Hz. noise.
With the aid of the LAS mini-computer system, the
character of this noise was studied and an analog
notch filter was designed. The effect of this filter
on the data and ultimately upon the diagnostic state-
ments of an ECG analysis program were greatly facili-
tated by means of the mini-computer system. The
optimal parameters (attenuation and window size) of
the filter could then be selected, in terms of a
trade-off between noise suppression and artifact
generation.

A general advantage of this system which has been
demonstrated before in other studies (ECG and pres-
sure from monkey preparations) is that an investigator

can automatically pre-process (edit, filter, and
digitize) dynamic physiologic data so that optimal
use of a large scale digital computer can be obtained.

Proposed Course:

The neurophysiological simulation work will be
extended to larger nets of cerebellar cells and
to other central nervous subsystems (e.g. walking
reflexes). It is also proposed to build a global
model of the cardiovascular system based on power
conversion and distribution; data (e.g. time course
of intraventricular pressure and volume) has already
been collected, which can be used for testing sub-
sections of the model. In the coming year the LAS
mini-computer system will be upgraded with the
addition of 16K core, a 1600 BPI magnetic tape drive,
a MAP 100 array processor, a disk pack, and a grey-
level CRT. It is anticipated that these improvements
will allow speedy investigation of image processing
schemes for nuclear medicine data (see 3.6).

Keywords:

neurophysiology, hybrid computer, simulation,
cerebellum, cardiovascular models, signal analysis,
electrocardiography, electromyography, image
processing.

Publications:

1. Pottala, E.W., and Mortimer, J.A.: A hybrid
    compartmental model for the alligator purkinje
    cell. 1: Preferred somatopetal conduction of
    dendritic spikes and soma-axon interaction.
    J. Neurosci. Res. (in press) 1975.

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Mathematical Modeling of Biological Processes

Previous Serial Number: 3.5

Principal Investigators: J. Fletcher, J. Rinzel (transferred
to NIAMD 2/1/75)

Co-Investigators: R. Lutz, BEIB, DRS; W. Rall, MRB, NIAMD

Man Years: Professional 1.8

Project Descriptions:

Background and Objectives:

The primary responsibility of the Applied Mathematics
Section is to provide DCRT and the NIH with high
level mathematical competence for biomathematical
modeling and data analysis. This competence includes
both theoretical and applied techniques, as well
as numerical computation methods. Each individual
in the section has a primary specialty in computer
science or mathematics, and in addition, each is a
capable programmer.

Project Tasks during FY 75:

1)   A Simulation Model for Substrate Supply in the
Microcirculation:

During FY 75, a new mathematical formulation of
substrate kinetics in capillary blood was discovered.
This formulation resulted in some simplification of
the model equations and permits the direct use of
the substrate dissociation curve rather than its
mathematical inverse which was used previously. In
this form, the model suggested that substrate transfer
to tissue was directly related to the slope of the
dissociation curve rather than its coordinate position
(P_{50} point) and subsequent modeling studies confirmed
this conjecture. A number of simulations were com-
pleted relating the effects of substrate kinetics

to tissue supply, and the role of 2-3 DPG in
modifying the oxygen-hemoglobin dissociation curve
in humans was examined. The simulation results were
presented at a recent international meeting, and a
publication will appear in the proceedings.

2) Dynamic Behavior of Mass Transfer in Pulsating
Laminar Tube Flow:

During FY 74, the collaboration of the Applied
Mathematics Section was requested in a project
directed toward the development and validation of
an experimental technique for the measurement of
mass transfer in tubes with pulsating flow. The
ultimate objective was a technique for measuring
shear stress in arteries and its possible relation-
ship in the formation of sclerotic lesions at
bifurcations. A brief literature survey revealed
that the commonly used approximations were inappro-
priate for the full model equations, while most
standard numerical methods were invalidated by the
mathematical singularity induced by the leading edge
of the imbedded electrode. During FY 75, a new
formulation was developed which removed this singular-
ity, thus posing the problem in a form more adaptable
to numerical solution. A new numerical solution
technique has been developed and is being tested for
its validity. Some preliminary results have been
presented at conferences and an application has been
published. Further work in this area will center on
validation of both experimental and theoretical results
and the development of a valid error analysis.

3) Mathematical Description of Cellular Neuroelectric
Signal Transmission:

The objectives of this study are to obtain biophysi-
cal understanding through mathematical modeling of
integration in a model dendritic neuron and of
impulse conduction along a model nerve axon. During
FY 75, a simplified version of the FitzHugh-Nagumo
nerve conduction model was used to study the phenomena
of active axonal conduction. Though it too yields
a nonlinear partial differential equation, its
traveling wave solutions can be obtained explicitly.
This permits a complete parametric description of its
solutions, which model a simplified ideal nerve
impulse, and periodic trains of pulses. The results
suggest that, for steady repetitive firing. the
propagation speed of a periodic train depends on
firing frequency. Additional numerical calculations

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are planned to further explore this dispersive aspect of nerve conduction.

As do other nerve conduction models, this simplified one has a multiplicity of traveling wave solutions. Such multiplicity is not found in experimental observations and has led several investigators to conjecture on the stability properties of these various waves. For the simple model, stability has been analyzed explicitly to verify the conjectures and to suggest which waves are likely to be observed. Two different stability notions are formulated: temporal stability, for perturbations generated at a single instant of time; and spatial stability, which may be continually applied in time, but spatially restricted to a fixed location. This is appropriate for many nerve signaling problems. Stability results for this simple model motivate their attempted extension to a general class of nerve conduction equations. Critical stability transition properties for these models have been analytically and parametrically examined. For periodic wave trains, maximum frequency was found to distinguish the transition from spatial stability to instability. A manuscript describing these results has been submitted.

Keywords:

applied mathematics, biomathematical modeling, numerical computation, simulation model, microcirculation, pulsating flow.

Publications:

1. Fletcher, J.E.: A model describing the unsteady transport of substrate to tissue from the microcirculation. SIAM. J. Applied Math., Vol. 29, No. 2, September 1975.

2. Lutz, R.J., Cannon, J.N., Fletcher, J.E., and Fry, D.L.: The measurement of wall shear stress in model arteries by an electrochemical technique. Proceedings of ACEMB, October 1974.

3. Fletcher, J.E.: Distributed parameter modeling of the microcirculation. Systems Analysis of Biomedical Transport, edited by D.D. Reneau, Marcel Dekker, Inc., New York (in press).

4. Rinzel, J.: Voltage transients in neuronal
    dendritic trees. <u>Federation Proc. 34</u>, 1350-1356,
    1975.

5. Rinzel, J., and Rall, W.: Transient response
    in a dendritic neuron model for current injected
    at one branch. <u>Biophys.J. 14</u>, 759-790, 1974.

6. Rinzel, J.: Spatial stability of traveling wave
    solutions of a nerve conduction equation.
    <u>Biophys. J.</u> (in press).

Project Title: General Mathematical and Computational
Collaborative Efforts

Previous Serial Number: 3.5

Principal Investigators: J. Ashbrook, E. Hill, J. Fletcher

Co-Investigators: A. Spector, Univ. of Iowa
R. Shrager, DCRT; R. Feldmann, DCRT;
H. Hoffman, Biometry Branch, NICHD;
W. Sperry, CCB, DCRT

Man Years: Professional - 2.2

Project Description:

1)   Modeling of Macromolecule-ligand Binding:

A study of the binding of physiologically important
long-chain fatty acids to human plasma albumin has
been completed and published.   Further work in this
area will concern displacement of albumin bound
ligands by drugs or other competing compounds.

2)   Low Weight for Age Study:

Computer software was completed for the generation
of contour plots of collected data.   The NICHD has
employed this software for the construction of contour
levels for bivariate distributions of birth weight
and gestational age by race, sex and metropolitan
status.   Details of resulting studies are described
in the reports of the Institutes concerned.   Additional
studies utilizing this software are currently being
conducted by the Biometry and Epidemiology Branches,
NICHD.

3)   Computer Generated Graphics and Display Systems:

Several new post-processors have been added to the
Integrated Plotting Package (IPP).   This new software
allows an IPP program to generate plots on any terminal
in the Tektronix 4010 family of graphic displays, or

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on a CalComp plotter attached to a remote job
entry (RJE) workstation in addition to the previously
supported plotting devices. Supporting software
was rewritten in American National Standard (ANS)
FORTRAN to preserve machine independence. The
software has been distributed to other computer
centers, and a user's guide is now in press.
Additional research is being conducted in collabor-
ation with CCB, DCRT in the general area of computer
generated graphics and textual data representation.

4) Simulation of Body Fluid Balances:

This project involves the implementation of inter-
active digital computer models designed to help
scientists study the interacting physiology of
major body systems in health and disease. A model
called MACPEE is being analyzed and implemented on
DCRT's PDP-10 and IBM System 370 computers. MACPEE
is a model of heart, circulation, body fluid compart-
ments, kidneys, and various hormones. This model
can be used to approximate most problems of renal
disease, body fluid disturbance or complex inter-
acting disorders such as nephrotic syndrome, heart
failure, Addison's disease, etc.

5) Image Processing of Nuclear Medicine Data:

Algorithms are being developed to extract features,
find edges, perform texture analysis, and find
profiles of digitized radioisotope distribution
patterns. These attributes will be used to classify
images as either normal or abnormal using an adaptive
supervisor. Discriminant analysis, classical pattern
recognition techniques, and other optimization tech-
niques are being used in developing such routines.

6) Energy Minimization of Protein Structures:

This project involves the integration of energy
minimization techniques into the body of DCRT's
molecular structure manipulation system. This
involves determining the best methods for doing
energy minimization and data structure manipulation
with respect to protein structures. A group of
computer programs that allow one to study the con-
formations of biological macromolecules is being
analyzed and implemented on the PDP-10 computer
system. The conformation is altered to minimize
an empirical energy function by moving all atoms by
the method of steepest descents. These techniques

are needed to refine coordinates obtained by X-Ray
Crystallography and thus improve the techniques of
stereochemistry.

Keywords:

mathematics, modeling, macromolecule-ligand binding,
graphical displays, graphics, simulation, image
processing, energy minimization, protein structures.

Publications:

1. Simpson, R.B., Ashbrook, J.D., Santos, E.C., and
    Spector, A.A.: Partition of fatty acids. Journal of
    Lipid Research, Vol. 15, pp. 415-422, July 1974.*

2. Hoffman, H.J., Stark, C.R., Lundin, F.E., Jr.,
    and Ashbrook, J.D.: Analysis of birth weight,
    gestational age, and fetal viability, U.S.
    births, 1968. Obstetrical and Gynecological
    Survey, Vol. 29, No. 9, pp. 651-681, September
    1974.

3. Ashbrook, J.D., Spector, A.A., Santos, E.C., and
    Fletcher, J.E.: Long chain fatty acid binding
    to human plasma albumin. Journal of Biological
    Chemistry, Vol. 250, No. 6, pp. 2333-2338,
    March 1975.

4. Ashbrook, J.D., and Sande, G.: A User's Guide
    to the Integrated Plotting Package. U.S. DHEW,
    PHS, NIH, DCRT, LAS. Wash., D.C., U.S. Govt.
    Print. Off., 1975, 120 pp.

*Reported in FY 74 as "in press".

Project Title: Statistical Research in Clinical Pathology

Previous Serial Number: 3.4

Principal Investigators: Eugene K. Harris, assisted by
                           G. Shakarji, DMB, DCRT

Co-Investigators: M. Healy, Clinical Research Centre, Medical
                    Research Council, England
                    S. Brown, Clinical Chemistry, Clinical
                    Research Centre, England
                    D. S. Young, Clinical Chemistry Service,
                    Clinical Center, NIH

May Years: Professional 0.5

Project Description:

    Background:

        The studies of variation in normal blood chemistries
        which form the background of this project have been
        amply discussed in earlier annual reports.

    Progress during FY 74, 75:

        This report covers two years because the principal
        investigator continued research in this area during
        assignment to the Clinical Research Centre near
        London in FY 74.   During the past two years attention
        has focussed on the development of statistical theory
        to evaluate 1) the use of population-based normal
        ranges in assessing individual laboratory tests, and
        2) use of previous measurements on the same individual
        to forecast and test a current measurement.   These
        issues have particular significance for the inter-
        pretation of results from periodic health examinations
        of presumably normal individuals or from more inten-
        sive serial studies of patients in clinical trials.
        Two papers have resulted so far: one referenced
        below and a second just completed and submitted for
        publication (April, 1975).   In addition, an extensive
        unpublished report was prepared on the use of

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statistical methods in analyzing serial measurements
on patients under intensive care following surgery,
myocardial infarction, or other traumatic experience.
Aims are rapid detection of eventual outcome.

To support this work, computing packages have been
developed for the storage, updating, retrieval and
statistical analysis of cumulative clinical data on
individuals. A general description and full docu-
mentation of these programs is now in preparation.
The storage, updating and retrieval programs have
been in routine operation for the past 2 years in the
Hypertension-Endocrine Laboratory of NHLI under Dr.
F. C. Bartter, and now contain information on upwards
of 100 patients. The full set of programs, including
analysis routines, are expected to be used very
shortly in the analysis of a serial study of normal
volunteers designed in cooperation with the Clinical
Chemistry Service of the Clinical Research Centre,
Harrow (London), England and completed during FY 75.
Data will be transmitted to NIH for analysis and a
joint report prepared.

Plans for FY 76:

During the coming year, documentation of the computing
programs mentioned above will be completed and in-
cluded in a technical report for general distribution.
Immediate application will be to the data from England
cited above. Later, it is expected to apply these
programs and supplemental theory to new data from
normal subjects including baseline measurement series
followed by single samples at periodic intervals.
Cooperative efforts are also expected with the
Clinical Chemistry Service of the Clinical Center in
the application of various statistical monitoring and
forecasting methods to the quality evaluation of new
high-volume, multichannel autoanalyzer machines,
possibly including a study of normal volunteers.
Thus, FY 76 will see an emphasis on the application
of theory developed during the preceding two years.

Keywords:

normal variations, inter-intra-individual variation,
baseline reference values, normal ranges, clinical
chemistry.

Publications:

1. Harris, E.K.: Effects of intra- and interindividual variation on the appropriate use of normal ranges. Clin. Chem., 20, 1535 (December, 1974).

July 1, 1974 through June 30, 1975

PHS-NIH

Division of Computer Research and Technology

Summary of Branch Activities   DCRT

Data   Management   Branch   J. Emmett Ward
                                                        Branch Chief

I.   SUMMARY

Providing practical solutions to complex research and
administrative computer data processing problems is still the
raison d'etre of the Data Management Branch (DMB).

Reasonable progress has been made in providing a useful
Clinical   Information   Utility.   This   effort   supports   the
Clinical Center's Office of Clinical and Management Systems by
providing clinical investigators with diversified methods for
reviewing and extracting clinical data from three available
sources: Clinical Pathology Laboratory, Discharge Diagnosis and
Census.   The linkage, retrieval and security functions of this
system are discussed under the Clinical Support Section's
summary.

The impact at NIH of a new approach to systems development
known as Data Base Management Systems (DBMS) has not been
established at this time. IBM's Information Management System
(IMS) is one of many such DBMS's currently marketed by software
vendors.   In a joint effort, the NCI and DMB have begun an
evaluation of this system. A data base developed by Stanford
Research Institute for an ongoing NCI study of potentially
hazardous compounds was transferred to NIH during the year.
DMB personnel adapted this data base to run under the IMS
Interactive Query Facility and NCI is now testing the
flexibility of this software to meet its needs. In an attempt
to examine the full IMS utility, DMB is in the process of
developing a Divisional Information System for Cancer Cause and
Prevention.

A critical review of DMB applications software facilities
resulted in a complete upgrade of the Recursive Macro Actuated
Generator (RMAG) to its latest version RMAG21.   This new
facility handles all varieties of record formats, eliminates
the need for intermediate reading of edit format data sets,
provides automatic blocking and deblocking and enables parsing
of input data in extremely flexible form. The overall impact
of this effort is easier programming, shorter execution times
and reduced costs. A complete rewrite and integration of all

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of the existing generator programs using RMAG21 is currently in process and should be available for final testing by mid-fall 1975.

The IBM STATPAK software, a package of 40 on-line statistical routines, was recoded to FORTRAN IV from BASIC and implemented under the Time Sharing Option. Current usage of this package exceeds 175/week.

During the past year, development of a data management and statistics package (DMSP) was undertaken. This package will be used to solve a variety of problems including editing, consistency checking, updating , selection, transformation, recoding, and elementary statistics. It is desirable to consolidate the solutions to these problems into a single package in order to make the computer easier to use.

Both problem-oriented and procedure-oriented statements are available to the user of DMSP. Problems in data management and statistics are generally solved using the problem-oriented statements; but in cases where such statements are not adequate, it is possible to resort to the procedural statements, which are like those found in conventional programming languages. It is therefore possible to circumvent the limitations inherent in general systems which do not employ a procedural language, and it is also possible to provide unsophisticated users with easy-to-use problem-oriented, statements not found in ordinary procedure-oriented languages.

A system has been completed to provide massive storage and retrieval of chemistry data for the Endocrinology Branch, NHLI. Complete demographic and the associated chemistry data on 75 patients have been stored on tape using this system. This data base will provide patient chemistry information for the NHLI staff. It will also provide data for statistical evaluations. Statistical analysis, to date, has included evaluations of time of blood as well as blood pressure data, and trend analysis to evaluate short-term effects on blood pressure of patients using certain drugs.

In collaboration with the NIAMDD Field Studies Section in Phoenix, Arizona, we are examining insulin responses in a relatively well-known Indian population. In another project Branch personnel are involved in orienting the research investigators in the NIAMD Field Studies Section in Phoenix, Arizona with statistical packages in DCRT, especially with the capabilities of the Statistical Analysis System. This orientation will provide them with tools to analyze large volumes of data representing relationships of insulin level to

oral glucose load in subjects with a wide spectrum of glucose tolerance among the Pima Indians (a group having an extremely high prevalence of diabetes). We have developed special procedures to in ure the proper evaluation and execution of computer runs and to reduce computer run time on the projects.

In an effort to assist patients who have had laryngectomies the Veterans Administration is examining individual self concepts using Q-technique. A self assessment of definable personality traits is provided by each patient. Then evaluations of these data are performed. Evaluations have included correlations between "actual self-concept" and ideal self-concept; "actual self-concept" and "other" self-concept; evaluation of self-acceptance, independence, and good emotional control; and evaluation of self-rejection, dependence, poor emotional control, and withdrawal.

DMB has been working with the Laboratory of Statistical and Mathematical Methodology to evaluate and to detail test all options of the Statistical Analysis System (SAS) in order to determine the algorithmic validity of all features. Data Management Branch Staff was briefed on SAS capabilities and the use of this package is proving to be very valuable in editing and analyzing data.

In collaboration with Dr. Eugene Harris of the Laboratory of Applied Studies analysis software has been developed to assist him in evaluating intra-individual variations in serum blood constituents. Major portions of this package are complete. It has the capability to compute and plot tests for normality, test multivariate normality for selected combinations of tests, estimate average intra-individual variance, calculate pairwise correlations, calculate selected multivariate normal regions, and estimate purely physiologic variance.

A set of programs was modified and fully tested, on our system, to perform spectral analysis of digitized input data. These programs were written at Johns Hopkins University Applied Physics Laboratory. The programs compute three main functions: the power of spectral density data to decompose into different frequency components; autocorrelation to examine data periodicity; and stationarity and normality to determine the suitability of the data to be represented by spectral analysis alone.

The applications programming summary is as follows:

Documentation and Systems Support Section

1. In processing Case Reports new procedures to more closely control the editing and balancing of data using computer runs and AUTOTAB were introduced this year and personnel in

the OD/ORA Office were trained to use them effectively. For Fiscal Year 1973 approximately 50% of the 137 output reports were produced using generated programs. At the present time the OD/ORA Office is considering only producing about 25 general summary tables for this fiscal year and supplying detailed information by use of Query and AUTOTAB to those requesting such reports.

2. Continued our support for esoteric CICS programs in the ARMS Personnel System. Turned interactive retrieval programs over to SAB Staff.

3. Interfaced the Opportunity Skills System with ARMS to facilitate update and reduce manual effort.

4. Set up a system to verify Central Account Numbers for DRS via OFM CAN tables.

5. To support various DRS Branch activities, we are currently designing and developing systems for maintaining and controlling the 1) Glassware Billing System, 2) the Small Animal Billing System and 3) the Planning System.

6. Developed an NEI Information System for all extramural programs including contracts via the DRG IMPAC System and manually entered data of additional interest. System provides update, edit, report and query facilities.

7. Established an on-line consultant file for the NHLI, which provides update, edit and query capabilities to facilitate the selection of team members for such things as site visits.

8. Currently developing an inventory system for the NHLI to control approximately 25,000 "cell line" vials stored in six freezers at various locations within the Laboratory of Biochemical Genetics.

9. Produced a Data File of Soviet Cytologists and Geneticists for NIEHS.

10. Currently producing Machine Readable and Searchable indices of the PHS-149 series: "Survey of Compounds which have been tested for Carcinogenic Activity" for NCI.

11. Developed some fifty-one report programs which provide inventory and natural history data on primates (CEBUS monkeys) used in the NINDS Herpes Study.

12. Currently designing a system to evaluate the Siperstein method of diagnosing diabetes. Current plan is to apply Siperstein's basement membrane theory to a known Pima Indian population and Caucasian normal control group. Drs. Siperstein and Williamson will provide input to the system in support of this NIAMD Field Studies Section evaluation.

13. Currently developing a system intended to correlate the incidence, morbidity and mortality of kidney and urinary tract disease with research need. The population being studied is the three armed services from January, 1971 through December, 1973.

14. Developed a Print Format Generator (PFG) for easy production of report programs from data layout sheet formats.

15. Case Data Preparation for NSF, OD/ORA.

16. KWIC Indices for the NIH Central Library, DRS/L.

17. NICHD Grant System.

18. Baltimore Cancer Research Center (BCRC) Study, NCI.

19. Lupus Study, NIAMD.

20. This section also supports Tablemaker and is responsible for reviewing all DMB documentation before it is released to NIH users.

Applied Systems Programming Sections

1. In support of the Type II Intervention Study for the Lipid Metabolism Branch, NHLI, continued our monitoring of all data base activities and provided several new reporting facilities.

2. Currently providing an interface between data base functions and the statistical segment for the Carcinogenesis Bioassay Data System.

3. Currently participating in a retrospective study of Cardiac Valve Replacements for the Clinical Surgery Branch, NHLI. The study involves the collection and analysis of various pre-and post-operative data on the more than one thousand patients who have had heart valves replaced at the NHLI.

4. Developed a completely new interactive system for the Emergency Virus Isolation Facility, NCI. All medical information on employees of the facility is now entered and retrieved in-house; this provides the facility with excellent security and privacy for all employee data.

5. Developed a computerized distribution list for the Grant and Contract Guide Distribution Center of DRG. The system creates, maintains, and selectively produces labels to be used in the distribution of the Grant and Contract Guide and/or any of its various supplements. Other NIH mailing list requirements have also been satisfied using this system.

6. Produced the 15 Federal Survey Tables depicting DHEW funding to institutions of higher education for Office of Resources Analysis, O.D.

7. Provided an indexed information system for the Research Analysis and Evaluation Branch, Division of Research Grants. The RAE branch has found that by indexing several different files, 1) Inventory of Clinical Trials; 2) Application for Grants; 3) NIH Grants Abstracts and 4) NIH Contracts Abstracts, with DMB's indexing programs and by searching the index files with DMB's index query program, they can very quickly satisfy questions relating to these data. Prior to the development of this technique data volume precluded quick access and retrieval.

8. Developed an NIH Central Registry of Biological Agents and Materials for the Environmental Services Branch, Division of Research Services. DMB is currently augmenting this ESB system to include carcinogenic chemicals in use at NIH.

9. Developed a pharmacy computer file system for the Clinical Center Pharmacy. The file contains drug product data on all drugs available through the Pharmacy.

10. Established a computerized data processing system for the Laboratory of Parasitic Diseases, NIAID. The system maintains all pertinent data on monkeys infected with malaria and mosquitos infected by feeding from the malaria infected monkeys. The study is intended to trace the life cycle of malaria.

11. Currently developing computerized grants information files for the Program Analysis and Evaluation Branch, Division of Cancer Grants, NCI.

12. Provided a Water Supply Systems Inventory facility for the Water Supply Branch, Environmental Protection Agency. This data processing system helps the EPA monitor the thousands

of water supply systems in the U.S. To date, there are approximately 46,000 water utilities on the master file. This accounts for approximately 138,000 water sources. The data source is a questionnaire distributed to each system. System data includes such things as treatment processes, capacities, sources, etc.

13. Implemented a system to produce the Journal of the National Cancer Institute (JNCI) for the Division of Cancer Cause and Prevention, NCI. The computerized system aids the Office of the Editor in Chief, JNCI in handling of data endemic to approximately 900 manuscripts per year submitted for publication in JNCI.

14. Provided programming support for the data collection and reporting segment of the Cigarette Condensate Study for the Etiology Branch, NCI.

15. Continued development of the complete inventory and retrieval system in support of the Institute of Laboratory Animal Resources (ILARS). This system is sponsored by the NCI.

16. Developed an International Activities and Personnel Monitoring System for Fogarty International Center.

Scientific Applications Section

1. In support of the Laboratory of Socio and Environmental Studies, NIMH, developed a generalized data management and statistical analysis system for psychological and physiological measures. Programs for handling heart rate and galvanic skin response are available, as is the ability to retrieve data from those measures using behavioral characteristics (or time) as the retrieval criteria. A statistical program produces summary statistics for single physiological measures and regression statistics for pairs of measures. During this fiscal year a program for identifying and flagging faulty data, programs which identify missing data and prevent erroneous data intervals from entering the statistical segment of the system, were developed. Future efforts include fine-tuning the user documentation and writing a routine for correcting of behavioral data.

2. Added nine new protocols to the Surgery Branch, NCI data files. Current plans call for retention of the operation data files and dropping the core and protocol data from the active system.

3. Currently developing a clinical patient followup file for the Surgery Branch. Using the DMB generators, programs were generated and modified for creating update transactions and for the update and edit functions. Retrieval programs and a print program which provides the physician with a summary of his patient's treatment history will be available soon. Plans for the future include changing the site and histology codes and the associated error checking routines when the new international cancer surgery coding scheme is available.

4. Continued support of the current awareness search for Clinical Biological Activities (CBAC). This service is still offered free of charge to all researchers at NIH and is run biweekly as tapes are received from Chemical Abstracts Service in Columbus, Ohio. Current plans are to drop retrospective searches in favor of timesharing systems. Programming effort to duplicate what is already offered by timesharing organizations precludes duplicate development. Use of timesharing services would also provide NIH reseachers access to CA Condensates, which reflects the entire 80 sections of CA, as well as easier, quicker access to CBAC.

   Completed first full year of support for current awareness search of Biosciences Information System (BIOSIS). Twice a month tapes are received from the Biological Abstracts Service and information is disseminated to the NIH community through the same vehicle as CBAC.

   Mr. Gillespie of the NIH Library has been the primary contact for NIH researchers wishing to search this data base; he submits their profiles to DMB for Current Awareness searching.

5. Continued support of the Survival System, which was originally developed to support the End Results in Cancer studies of NCI and now serves other NIH Institutes.

   During the year several new requests for copies of the system by organizations outside the NIH were satisfied.

   The next submission of data will involve changes in format and data code values making it necessary to modify the Survival System to reflect these changes.

6. Initiated work on the survival or life table analysis for the Cutting Oil Study. This system supports the efforts of the National Institute of Occupational Safety and Health. It is a study relating job type to mortality and morbidity of cutting oil workers. A data base has been established, and preliminary frequency tables have been produced.

7. Revised the programs which evaluate the daily scintillation counter output of radioimmunoassays for NICHD. Periodic revisions are necessary to keep pace with changing theory and methodology. In addition the plot portion of the system was replaced by a new printer plot capability.

8. Developed a cataloging system for sera and the multiple tests run on them for the Surgery Branch, NCI. Retrieval is possible by cancer site, histology, patient number and name. Time for collecting a representative batch of sera for desired lab tests has been cut from 14 hours to one hour.

9. Continued support of the Mass Spectral Retrieval System, in collaboration with Dr. Fales, Laboratory of Chemistry, NHLI.

   During FY 75, a new data file, which increased the number of spectra from 12,000 to 28,000 was put up despite severe interface problems between the system's two computers. A 17-tape file of spectra sorted by peak was also put up. The fiche generation program was updated and successfully run, a new option was added to the search, and a number of problems were uncovered and removed. A new data file which will raise the number of spectra to 35,000 is being worked on currently. When purified, subsets of the new file will be made available as the complete file is too large for present hardware. Maintenance documentation of the system is being completed.

10. Developed a program, which provides plots and quality control statistics for laboratory experiments having to do with radioimmunoassays, for the Reproduction Research Branch, NICHD.

    After a period of use in the lab, more tests will be added to the program.

11. In collaboration with Dr. Rodbard, Reproduction Research Branch, NICHD, modified a package of programs which do peak detection and non-linear curve-fitting analysis on chromatographic data. Several options for clumping and smoothing of data points have been added and a plot capability included in the package.

    Future plans for this package include the development of a preprocessor for deriving initial values from computer examination of data, a histogram to aid in making manual decisions on initial values, and addition of other equations, e.g., log-normal, to the curve-fitter program which now is used in the Gaussian mode.

12. Began development for the analysis phase of the Carcinogenesis Bioassay Data System. This involves data from ongoing bioassay experiments in mice. The immediate aim is to detect previously unidentified carcinogens. During the next fiscal year a statistical description program giving counts of animals with specific pathologies, and a program generating regular survival curves, Kaplan-Meier curves, and the Breslow statistic will be incorporated into a terminal-driven analysis system, which will build (in the conversational mode) parameter cards and JCL for batch runs.

13. Redesigned the format of the drug file for the Division of Cancer Treatment. This data set, which contains cost information on clinical trials and preclinical screening of drugs, required new variables and new codes for existing variables. A data edit and update program was generated and a report summarizing the input data was provided. Also to be completed are four other summary reports. Future plans include addition of data retrieval via a CRT.

14. Provided programs for performing analytic calculations on scintillation counter data and plotting the manipulated data for the Laboratory of Chemistry, NIAMD. Future plans include adding new input formats whenever new instruments are purchased, and adding more efficient correction equations as new types of experiments are undertaken.

15. Developed programs to provide summary statistics on Mirex pesticide residue potency and exposure time for the Department of Agriculture. It was also necessary to create a reformatted tape with generated fields. Statistical analysis of this data (e.g., regressions) is taking place at the Department of Agriculture and the EPA.

16. Provided Wylbur-oriented data collection and search procedure for Dr. Freese, NINDS, to allow him to access by computer a collection of about 10,000 paper and journal citations.

17. Assisted Dr. Reichert, Laboratory of Neurochemistry, NINDS, in developing a data file to best utilize DCRT computer facilities for data analysis of sound-induced epilepsy. Laboratory of Statistical and Mathematical Methodology, DCRT, is providing statistical advice.

18. Completed development of a data base of journal abstracts from the literature of gastroenterology. Reformat and print programs were written. The CRAC system was utilized for searching the text. This is a pilot project to determine the usefulness of computerizing this data base. A number of searches were run on the data base in order to

explore the completeness of the file and the utility of the search. This experience indicates that automatic searching would not be cost effective at this time, and that a manual search is adequate. Running the Concordance program on the data base to produce a KWIC index for manual searching is the direction currently being explored.

19. Provided analysis and statistical programming support for the Type II Coronary Intervention Study.

20. Converted five PL/I programs from F-level compiler to Optimiz-Optimizing compiler for NLM's Toxline Data Base. One program was incomplete and required that an additional module be written.

Clinical Support Section

THE INFORMATION SYSTEM

During the past year the Clinical Support Section, in collaboration with Dr. Sharma, NIAMDD, has developed new modules for a planning and forecasting system, and conceptually, has improved the structure and utility of the system. The new modules are defined as follows:

. PERSONNEL Module - This module permits the operator to retrieve user-selected information in the field of personnel for decision-making purposes. The selections are made using the output selection sub-module which permits the user to display all or specific parameters from the unit record.

. PROJECT Module - The PROJECT Module displays selected information from three major sources: allotment allowance registry, object classification data, and program and monetary data.

. TRACKING - In the planning area, a module was developed that permits the collection, processing, recording, and displaying of program information for administrative and management purposes. The TRACKING Module was developed using the following assumption: the planning phase goes through many stages, and managers would like to recall, manipulate, and display various changes, additions and modifications made to programs in the planning phase.

Functional descriptions of the older modules of this system are:

. PROJECTION - This module displays contract and grant information in a very special way: using a base year and a selection strategy, the module will project over a six-year period monetary requirements for the defined time period and area specified.

. RETRIEVAL - The RETRIEVAL Module displays contract and grant information in a matrix format. The basic information displayed may be characterized as a profile of grants and contracts in a selected area.

.SUPPORT Modules - These modules are simply support programs designed for system maintenance purposes.

Since this system was designed to be operated on-line and interactively, some work was done to improve the display of operational information. Each module has uniquely defined commands with positioning selection parameters for defining retrievals. These commands and selection parameters form sub-modules within each major module, and are used to extract subsets of a given data base for display.

A HELP Command was developed that permits the user to display information on how to operate a user-selected module or specific command within the selected module. This developmental work was done using BNF Notions not only for assisting the user, but to document the module.

THE CLINICAL CENTER PROJECT

The improvement of the availability of clinical data to the NIH research community has been our primary concern this past year. This task was done through the expansion of data coverage and the completion, of our initial concept of a Clinical Information Utility (CIU).

Presently, there are three clinical data sources: clinical pathology laboratory data, discharge diagnosis and census data. Although only two of these data sources are accessed using the CIU System, clinical pathology laboratory and discharge diagnosis data, techniques have been defined which permit the retrieval of census data within the CIU structure.

The Clinical Information Utility System is a special data base management system that accesses clinical data by patient hospital numbers, data coded elements or a logical expression of data coded elements. The access by patient hospital numbers is simply a direct procedure that permits the retrieval of all or subsets of patient data.

The most powerful accessing technique of clinical data is performed by defining a patient set using Boolean logic. This procedure allows the user to define a set of patients using data coded elements from clinical pathology laboratory data, discharge diagnosis or both. The data coded elements are laboratory test codes and ICDA codes.

The Boolean logic accessing technique is made possible by simply inverting the files on the data coded elements, i.e., the keys in the inverted files are the data coded element. The unit record, uniquely defined, contains all patients that have had a given test or all patients that were discharged and assigned a specific ICDA code.

The Boolean logic module uses RMAG, a data support system developed in the Data Management Branch. All of the Boolean operators can be used for defining a selection strategy.

The Privacy Bill requires all systems accessing Federal Data Bases to maintain a log-file. In this log-file, the systems must record the following information:

a) Who accessed the data?
b) When was the data accessed?
c) Why was the data accessed?
d) What data was retrieved?

This feature was defined and implemented this past year for recording the above information. The Privacy questions are answered by simply running an inquiry using IRS to retrieve the requested information from the log-file.

Administratively, CIU is operated by the Clinical Center Staff, OCAMS. Access to the data base is approved by OCAMS. This office will request answers to the questions previously stated on Privacy for recording into the log-file. Other information such as accounting and type of retrieval will be requested for the completion of access privileges.

The search parameters that are used for retrieval purposes are as follows:

a) patient hospital number
b) data coded elements
c) date or date range
d) test value or value range.

In general the types of retrievals that may be defined are : a) All data on specific tests for a list of patients; b) All data on for a list of patients; c) all discharge diagnoses on a list patients; and d) any combination of search parameters.

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Software Support Section

As discussed in the Branch summary, RMAG21 has been developed this year and all of the DMB generators are being redesigned and implemented using this flexible software.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities   1.   DCRT

2.   LABORATORY OF STATISTICAL AND MATHEMATICAL   3.   James E. Mosimann
     METHODOLOGY   Chief

1.   INTRODUCTION

In its initial year of activity, the Laboratory of Statistical and Mathe-
matical Methodology (LSM) developed its role of service in statistics,
mathematics, and computer science for the NIH community. First priority was
given to the establishment of computational and consultative services
available to any member of NIH. New program packages of statistical and
mathematical routines were implemented, and an active program of consultation
was initiated. The description of computational and consultative services is
outlined in sections 2 and 3, respectively. Some consultative services
resulted in close collaboration of LSM staff with the investigator, and joint
publication of results occurred.

LSM's own research activity is indicated in section 4. This activity is
essential, since a program of consultation and service like that of LSM
requires highly skilled professionals in statistics, mathematics and computer
science.

2.   COMPUTATIONAL SERVICES OF LSM

An important part of LSM's activity is the implementation and maintenance of
statistical and mathematical program packages for the NIH user community.
These packages offer a variety of programs to the user.

In addition to those previously available, four packages have been newly
installed on the IBM 370. These are: SAS, the Statistical Analysis System
from North Carolina State; IMSL, the International Mathematical and
Statistical Library; PSTAT, the Princeton Statistical Package; and BMDP, the
new UCLA Biomed series of programs. Along with the old BMD series, which will
still be offered, and the NIH program collection known as MSTAT1, a broad
statistical and mathematical capability is now available to 370 users.

Each package has its own characteristics and advantages. Some attractive
features of SAS are the ease of use, convenient analysis of subsets of a data-
set, and simplicity in editing, modifying and transforming data. SAS and
WYLBUR are particularly compatible since SAS statements are column-independent.
SAS is usable by anyone willing to learn a few procedure statements. The IMSL
library comprises about 400 mathematical and statistical routines. Unlike SAS,

the user writes his own main routine to call these. A strong point of this library is its use of up-to-date numerical algorithms. PSTAT, the Princeton statistical package, offers programs that will perform multivariate analyses on large databases involving many variables.

The use of LSM-supported statistical and mathematical packages at NIH is considerable. Routines of the BMD package had an average of over 600 user-accesses per month during the past year (low, 430; high, 890). The new BMDP series was implemented at the end of the fiscal year, and counts of its use are not yet available. SAS, a new package, has shown steady growth in use. Accesses for the last four months have climbed as follows: 220, 320, 480, 530. This system now has close to 200 users. As an example of a package used for specialized but essential purposes, PSTAT had an average of 10 accesses per month. Since IMSL is a subroutine library, counts are not available. The old math/stat library MSTAT1 had 900 accesses per month in the first half of the year. Unfortunately, comparable counts are not available for the second half of the year.

Important packages in the mathematical modeling area are MODELAIDE (S/370) and MLAB (PDP-10). Both packages receive wide use at NIH and elsewhere. Their authors are currently with LSM. Both the authors of MODELAIDE and MLAB are active in consultation and collaboration with NIH users. Both systems have been exported internationally and domestically to a variety of institutions. Most recently, the SUMEX computer project at the Stanford Medical School is providing MLAB to its users.

In the past year, a new MLAB manual (the 5th edition) has been prepared and is available. MLAB is promoted with demonstrations and courses. This system provides an interactive mathematical modeling capability with extensive graphical capability.

3. CONSULTATIVE SERVICES OF LSM

The consultative services of LSM range in subject and scope from answering a question about the job control language needed for a particular program package, to the development of statistical methods and models for data analysis for a particular experiment.

Specific consulting activity is defined as activity directly and consciously devoted to the needs of a specific user outside LSM. Hours devoted to direct consulting by LSM during the year are given below. Of course, other LSM activities underlie and support the direct consulting; for example, installation and maintenance of statistical packages requires considerable time which does not appear as direct consulting.

LSM averaged 550 hours per month of specific consulting out of 1600 total hours. All NIH institutes except NIGMS are represented in these hours. Eighty-five percent of LSM's specific consulting was directly to users outside DCRT. The remainder was also directed to users outside DCRT, but through the intermediary of non-LSM, DCRT staff.

Of the total hours, 20 percent involved largely mathematical or statistical advice with little computer use; 40 percent involved mathematical and statistical advice alongside considerable computer use; 40 percent involved mostly computation with little or no mathematical or statistical advice.

A major service of LSM consulting is responding to trouble-shooting questions rapidly and efficiently. Just over 50 percent of specific consulting activities involved sessions of one hour or less; and just over 80 percent, 4 hours or less. Availability of staff for the rapid resolution of user problems is a prime concern of LSM.

Of those jobs requiring more than four hours, many represent a sizeable effort on the part of LSM staff. The following list gives some indication of the variety of such projects.

1. J. Bieri and R. Evarts, LNE, NIAMD. Evaluation of the Vitamin E activity of gamma-tocopherol relative to alpha-tocopherol. Consultation was done on the analysis of experimental data to assess the relative potency of gamma-tocopherol as well as on the statistical principles underlying parallel line bioassays.

2. V. Bono, DE, NCI. Evaluation of chemotherapy drug assays. Computer models were developed and implemented for the analysis of cell DNA content, as revealed in histograms obtained from drug-treated tissue culture preparations. Therapeutic and non-therapeutic drug effects were contrasted.

3. A. Cheever, LPD, NIAID. Study of the effects of schistomiasis using autopsy data. A large file was organized. Numerous tables were produced. Discriminant and other analyses were performed. To date, association of egg and worms burden by anatomical site with pathological conditions have been studied.

4. B. Chock, LB, NHLI. Cascading enzyme systems. A system of cascading enzymes is simulated using MODELAIDE.

5. J. Folk and R. Chung, LB, NIDR. Activation and inhibition of clotting factor XIII. Mechanisms of action are being modeled.

6. M. Geier, LGCB, NIMH. Maintenance of data analysis software. Computer programs for evaluation and display of laboratory data were maintained, and user assistance provided as needed.

7. V. Geoffrey, IR, NINDS. Study of dystonia. Analysis of time intervals comprising sequences of speech, dystonia, speech, ... Calcomp programs were written for graphic display of the sequences over time. A large FORTRAN program generated tables of data cross-classified and grouped. Various descriptive statistics were generated by use of packaged programs.

8. V. Geoffrey, IR, NINDS. Parkinsonian patients. Accelerometer observations were made on speech sounds under two different treatments. The association of accelerometer variables with treatment was studied, assisted by Karen Pettigrew, NIMH. A package profile analysis, in conjunction with editing and other package programs was employed.

9. R. Ginsberg, EFS, NIAMD. Investigation of the effect of phenobarbital on biliary lipid metabolism in man. Biliary parameters were measured before and after administering the drug. Statistical tests of significance were performed to determine whether differences existed between the means of the biliary parameters before and after administration of phenobarbital.

10. R. Hamman, EFS, NIAMDD. Data on diabetes patients. Several days' study of BMDX76 (Survival Curve Program) to interpret options and output.

11. R. Hamman, EFS, NIAMDD. Time-in-study without a positive glucose tolerance test: subjects from a population with high incidence of diabetes. Age/sex/weight were cross-classified and compared. A FORTRAN program was devised.

12. R. Hendler, LB, NHLI. Oxidation of cytochromes. A paper has been completed using the non-linear fitting procedures of MLAB.

13. R. Hendler, LB, NHLI. Mathematical modeling. A paper on oxidation of cytochromes is now in print. Models for an improved multi-channel technique for resolving absorption data into chemical species are being considered. Also, models for DNA damage and repair are under discussion.

14. C. Hoover, DCBR, NIMH. Marital conflict in manic-depressive patients. The investigator is attempting to isolate factors in marital conflict which differentiate patients from their spouses or distinguish between diagnostic subclassifications of manic-depressive illness. Thus far, discriminant analysis has been the principal statistical method employed. A program has been written to evaluate discriminant functions calculated by the BMD series discriminant analysis program.

15. L. Keefer, CMT, NCI. Investigation of the hydrolysis of methyl (acetooxymethyl) nitrosamine (DMN-OAc) to the presumed carcinogenic metabolite of dimethylnitrosamine (DMN-OH). In order to determine the uniform consumption rate of the starting material and a uniform disappearance rate of the total nitrosamines, regression analyses were performed.

16. L. Kohn; R. Tate; L. Leive, LBP, NIAMD. Two counter scintillation. A mathematical solution for the optimum position of a discriminator between carbon and tritium channels was obtained.

17. L. Kvols, BC, NCI. Duration of remission and mortality data for Hodgkin's disease. Several analyses were made using the Breslow program.

18. C. Maloney, BOB, FDA. Pertussis potency tests. This project involves the development of statistical programs for use in the comprehensive examination of the potency and safety testing of pertussis vaccines by the Bureau of Biologics. Findings have led to innovations in testing procedures.

19. C. Maloney, BOB, FDA. Bioassay. This project involves evaluation of different computational methods in an effort to refine the assessment of biologics products. A bioassay program with a number computes either probits or logits with options for individual and/or pooled slopes, with or without conversion of, and a test for parallelism in relative potency has been written.

20. N. Matheson, EM, NLM. The impact of a one-year grants program on hospital library development. A master file was created, and programs to generate new variables were written. These were interfaced with the Statistical Analysis System (SAS) which was employed to calculate a large volume of descriptive statistics and tables. Ms. Matheson's report concluded that the grants program had had a statistically significant effect on the development of hospital libraries.

21. E. Mihalyi and D. Towne, LB, NHLI. Kinetics of Fibrinogen digestion. A fourth paper in a series on this topic has been completed. The analyses involved extensive use of MODELAIDE.

22. R. Peabody, DIR, CC. Interview scheduling. LSM has assumed the responsibility of preparing and running the interview scheduling system for the NIH Associate Program of the Clinical Center. This system, which schedules the applicants for interviews, prints acceptance letters, interview, applicant, and master schedules, is run each spring.

23. H. Pettigrew, B, NCI. Small-rodent carcinogen-bioassay experiments. The analyses employed survival curve methods. Modification of a previously existing Breslow program, and study of the literature on survival curves was performed.

24. W. Reichert, LNC, NINDS. Study of sound exposure and audiogenic seizure on cerebral ATPase activity in mice. Comparisons of enzyme activity in sound-exposed and control mice of two strains were made using analysis of variance and t-tests. Data were first standardized by litter. Reichert has finished a paper on this work.

25. D. Reiss, APB, NIMH. Multi-family group study. This study concerns disturbed adolescents and their families. There are four major types of data: "who-to-whom" speech data, cohesiveness questionnaire data, sociometry data, seating position data. Data for this study is voluminous. Although programs for each type of data are completed, maintenance and data processing does require considerable effort. Dr. Reiss is now with the Center for Family Research, George Washington University.

26.   P. Savage, EFS, NIAMDD. Discriminant analysis of diabetes-related variables in patients with and without retinopathy.

27.   P. Savage, LFS, NIAMDD. Multivariate observations on diabetes patients. Queries on mathematical models were handled and multiple and partial correlation and regressions were performed. Relevant literature was reviewed. Interpretation of SAS options and outputs in regression and correlation programs was given.

28.   K. Smith, VR, DRS. Selection for body weight in mice. Statistical programs have been written for this study which are directed toward providing an objective evaluation of the effects upon genetic variation in inbred strains of mice.

29.   G. Spellman, CP, CC. Effect on clotting of varying amounts of red cell protein. Extensive editing and package programs were used in conjunction with mathematical modeling by Karen Pettigrew, NIMH.

4.   RESEARCH ACTIVITIES OF LSM

The LSM computational and consultative activities place highly qualified mathematicians, statisticians and computer scientists at the service of the biomedical community. LSM specialists must exhibit an up-to-date knowledge of their subject matter fields at the research level. Research activities within LSM in mathematics, statistics, or computer science (1) either spring directly from NIH problems which require new explorations in these fields or (2) contribute in a major way to the development of the staff member's excellence in the field for which he is responsible.

The LSM research effort averaged 500 hours per month. About 50 percent of these hours are in support of direct consulting activities. Individual projects follow.

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Pattern Recognition

Previous Serial Number: None

Principal Investigator: Marvin B. Shapiro

Other Investigators: David Symmes (NICHHD)

Cooperating Units: None

Man Years:
          Total: 0.5
          Professional: 0.5
          Others: 0.0

Project Description:

   Objective:

      The development of a set of pattern recognition computer programs for
      use in biomedical research.

   Methods:

      A variety of pattern recognition techniques are being implemented for
      the PDP-10 computer. These techniques include the computer learning
      machine, the minimal spanning tree algorithm, non-linear mapping methods,
      feature selection, and nearest neighbor analysis.

   Major Findings:

      (1) Both learning machine and cluster analysis techniques were applied
      to an analysis of monkey vocalization patterns. Results clearly showed
      that the patterns for each individual monkey clustered together and that
      patterns for a given monkey can be recognized as different from those of
      other monkeys.

      (2) An algorithm was developed which considerably improved the
      efficiency of the nearest neighbor method, a widely used pattern
      classification technique.

(3) Learning machine and nearest neighbor classification techniques
were applied to predicting the activity of cancer anti-tumor drugs
based on substructural features. Using a training set of 138 drugs
containing 421 different substructural features of three types -
augmented atoms, ring structures, and paths between heteroatoms - a
prediction rate of 80 - 90 percent was obtained on a test set of 24
drugs of unknown activity.

Significance to Biomedical Research:

The recently developed field of pattern recognition offers important new
approaches to organizing and analyzing biomedical data. Especially
important is its ability to find unexpected relations among data. To
display multidimensional data, to analyze features in data are other
important benefits.

Proposed Course:

The programs already developed plus a number of other important methods
will be collected into a package designed for general use on the PDP-10
computer. A manual describing the package will be written and distributed.

Keywords:

pattern recognition, cluster analysis, learning machine, nearest neighbor
classification, feature extraction

Honors or Awards: None

Publications:

Chu, K. C., Feldmann, R. J., Shapiro, M. B., Hazard, G. F., Geran, R. I.:
Pattern Recognition and Structure-activity Relationship Studies. Computer-
assisted Prediction of Antitumor Activity in Structurally Diverse Drugs in
an Experimental Mouse Brain Tumor System. J. Med. Chem., June, 1975.

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Research Topics in Computer Science

Previous Serial Number: None

Principal Investigator: Gary D. Knott

Other Investigators: None

Cooperating Units: None

Man Years:
Total:	0.7
Professional:	0.5
Others:	0.2

Project Description:

The object of this project is to develop theoretical bases for new computer methods which will expand and improve its use in biomedical computation. The methods used are the application of known and the development of new pertinent theorems from combinatoric and other related mathematics. Research work in storage and retrieval algorithms and their efficiency has been the primary topic of concern. A Ph. D. thesis on deletion in binary storage trees has resulted from this research and is cited in the publications list below. This research will culminate in several further publications in the future. Other work concerns a numbering system for permutations of combinations cited below.

Research on Operating Systems Interprocess Communications has been done, resulting in a two-part publication on a proposal for such a facility in Operating Systems Review (cited below) and in the presentation of this work at the recent workshop on interprocess communications sponsored by SIGOPS and SIGCOMM of the ACM.

Optimal item orderings in split hashing schemes and certain interesting algebraic characterizations of fixed permutation open addressing methods are currently being studied.

These methods have and continue to improve the efficiency of computers in biomedicine and make new applications possible.

Keyword Descriptors:

computer science, storage and retrieval, operating systems

Honors and Awards: None

Publications:

Knott, Gary D.: "A Numbering System for Permutations of Combinations", CACM, to appear, 1975.

Knott, Gary D.: Deletion in Binary Storage Trees, Ph. D. thesis, Stanford University, Computer Science Department, 1975.

Knott, Gary D.: "A Proposal for Certain Process Management and Inter-process Communication Primitives, Part I", Op. Sys. Review, Vol. 8, No. 4, pp. 7-44, October 1974.

Knott, Gary D.: "A Proposal for Certain Process Management and Inter-process Communication Primitives, Part II," Op. Sys. Review, Vol. 9, No. 1, pp. 19-41, January 1975.

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Nonlinear Equations

Previous Serial Number: None

Principal Investigator: Richard I. Shrager

Other Investigators: Gary D. Knott (LSM, DCRT)
                       Edward Hill (LAS, DCRT)
                       John E. Fletcher (LAS, DCRT)
                       J. Douglas Ashbrook (LAS, DCRT)

Cooperating Units: DCRT, Laboratory of Applied Studies

Man Years:
            Total: 1.0
            Professional: 1.0
            Others: 0.0

Project Description:

    Objective:

        To develop methods for solving nonlinear equations frequently encountered
        at NIH.

    Methods:

        A continuing effort is made to create methods or extend existing methods
        to solve problems in a host of NIH applications, and to make those
        methods available in convenient computer programs or routines, such as
        MODELAIDE and MLAB.

    Major Findings:
        a) Marquardt's method for nonlinear least squares was extended to
            handle linear constraints.
        b) A suitable error analysis was devised for constrained parameters.
        c) A method for solving nonlinear stiff differential equations was
            adapted to computer from a Ph. D. thesis of Kai-Wen Tu.
        d) Marquardt's method, see (a), is now being extended to norms other
            than least squares. Preliminary results are promising.

Significance to Biomedical Research:

These methods are now being applied to problems in human metabolism, cell growth, chemical kinetics, and spectral analysis (UV, IR, CD, ORD, NMR, ESR).

Proposed Course:

As the methods are proved in test and practice, they will be incorporated into easy-to-use systems like MLAB, and as a result, the systems themselves should evolve to do more useful work with both less human and less machine effort.

Keyword Descriptors:

nonlinear, parameter estimation, least squares, stiff differential equations, linear programming, quadratic programming, minimax approximation, error analysis

Honors and Awards: None

Publications:

R. I. Shrager: Constraint analysis in model building. Proceedings of the Fifth (1974) Annual Pittsburgh Conference on Modeling and Simulation, Part 2, 991-996, Instrument Soc. of America, 1975.

D. E. Blumenfeld, R. I. Shrager, G. H. Weiss: Spatial distributions of homes for journeys to work by different modes of transportation. Transportation Res., 9, 1, 19-23 (February 1975).

R. W. Hendler, D. W. Towne, R. I. Shrager: Redox properties of b-type cytochromes in Eschericia Coli and rat liver mitochondria and techniques for their analysis. Biochimica et Biophysica Acta, 376, 42-62, 1975.

I. G. Darvey, R. Shrager, L. D. Kohn: Integrated steady state rate equations and the determination of individual rate constants. J. Biol. Chem., (in press).

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Discrete Mathematics and Applications

Previous Serial Number: None

Principal Investigator: George Hutchinson

Other Investigators: None

Cooperating Units: None

Man Years:
            Total: 0.5
            Professional: 0.5
            Others: 0.0

Project Description:

   Objectives:

      To make new mathematical methods, techniques and discoveries in discrete
      mathematics available and explore their application to biomathematics
      and computers.

   Major Findings:

      Advances were made in demonstration of recursive unsolvability of
      certain classes of problems concerning subspaces of a vector space.   (In
      effect, no computer program can be written to solve this particular
      problem in a general way.)   It was demonstrated that certain related
      classes of problems were solvable, and that the order relationships
      between arbitrarily many subspaces of a vector space can be reduced to
      their study between five subspaces.

   Significance to Biomedical Research and the Program of the Division:

      Contribution to mathematical research and constrains computer solutions
      to a wide class of applied biomathematical research.

Proposed Course:

An earlier study applying linear inequalities to chemical reaction systems will be revised for publication. Mathematical findings are now being edited and followup studies in preparation. Further development of chemical reaction system analysis will be considered, and new applications explored.

Keyword Descriptors:

linear algebra, modular lattices, linear inequalities, chemical diagrams

Honors and Awards: None

Publications:

Hutchinson, G.: On the representation of lattices by modules. Trans. Amer. Math. Soc. (In press).

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Visual and Biological Shape

Previous Serial Number: DCRT 1.1

Principal Investigator: Harry Blum

Other Investigators: Virgil Carlson (NIMH)
                      Brian Murphy (NIMH & U. of Md.)
                      Richard L. Webber (NIDR)

Cooperating Units: NIMH, Laboratory of Psychology and Psychopathology
                    NIDR, Clin. Invest. and Research Serv. Branch

Man Years:
        Total: 0.6
        Professional: 0.6
        Others: 0.0

Project Description:

The overall objective of this project is to develop a formal descriptive
language applicable to biological shapes and apply this language to the
variety of problems arising in biology and medicine: taxonomy, neurobiology
and organismic development. This would permit a better modeling, hence
understanding of these processes and also allow for the automation of many
shape processes now done by humans.

The method employed stems primarily from a new geometry conceived by the
principal investigator. It is applied to a variety of problems, both to
clarify the biological processes taking place and to develop the mathematics
in biologically relevant directions. These have included cells and tissues
from light microscopy, skeletal descriptions in growing organisms, chromosome
description, visual psychophysics and visual neurophysiology.

A major accomplishment this year is the setting up of an experimental proce-
dure for doing shape psychophysics on amorphous forms by humans. Other
major accomplishments deal with theoretical developments to allow implementa
tion of such a geometry on a computer. These are: (1) the development of
a method for getting proper description on a computer without sacrificing
the smoothness of the forms, (2) the extension of the method to forms that

are specified by gray scale pictures and (3) the extension of the methods to the description of 3-dimensional forms.

Anticipated work next year includes the continued experiments on visual psychophysics of amorphous forms, continued descriptive work on skeletal forms, continued implementation of the theory to computer implementation, and finishing of the application to the theory of shape processing in the vertebrate visual system.

Keyword Descriptors:

biological shape, biomathematics, geometry, taxonomy, developmental biology, visual psychology, visual physiology, nervous system models

Honors and Awards: None

Publications:

Blum, H.: A Geometry for Biology. In Gurel, O. (Ed.): Mathematical Analysis of Fundamental Biological Phenomena. Annals of the New York Academy of Sciences, Vol. 231, pp. 19-30,1974.

PHS-NIH
Individual Project Report
July 1, 1974 through June 30, 1975

Project Title: Multivariate Statistical Methods

Previous Serial Number: None

Principal Investigator: James E. Mosimann

Other Investigators: Cecelia B. Clark (Project Stride)

Cooperating Units: None

Man Years:
Total:	0.2
Professional:	0.2
Others:	0.0

Project Description:

The overall objective of this project is the study of multivariate statis-
tical methods for the analysis of data which take the form of ratios or
proportions. Included is a study of properties of the multivariate log-
normal distribution in the analysis of ratios. This distribution has broad
applicability to biomedical data at NIH.

Keyword Descriptors:

size variable, shape vector, multivariate lognormal distribution, gamma
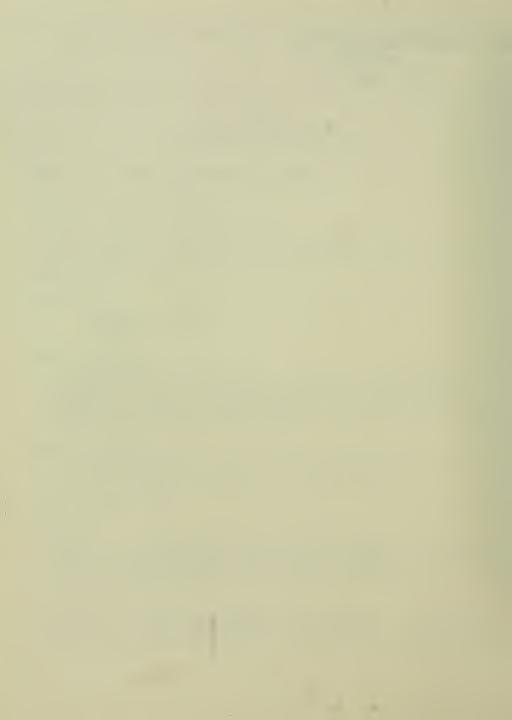distribution, Dirichlet distribution, constrained variables

Honors and Awards: None

Publications:

Mosimann, J. E.: Statistical Problems of Size and Shape. I. Biological
Applications and Basic Theorems. In Statistical Distributions in Scientific
Work, Vol. 2, Model Building and Model Selection, G. P. Patil, S. Kotz, and
J. K. Ord, eds. pp. 187-218, D. Reidel Publishing Company, Boston,
Massachusetts, 1975.

Mosimann, J. E.: Statistical Problems of Size and Shape. II. Characteriza-
tions of the Lognormal, Gamma and Dirichlet Distributions. In Statistical
Distributions in Scientific Work, Vol. 2, Model Building and Model Selection,

G. P. Patil, S. Kotz, and J. K. Ord, eds. pp. 219-240, D. Reidel Publishing
Company, Boston, Massachusetts, 1975.

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY
Report of Program Activities
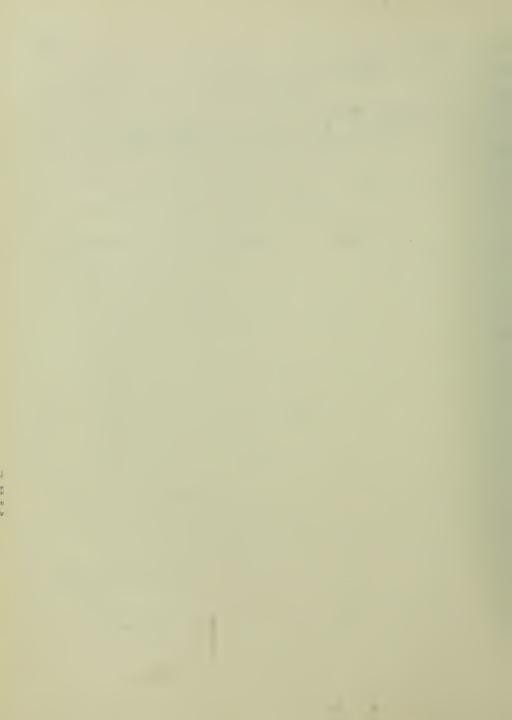July 1, 1975 through June 30, 1976

ANNUAL REPORT

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Director's Summary

The Division was established in 1964 to make the rich potential of an emerging computer technology available to biomedical research and administration at NIH. It embodies expertise in electronic engineering and computer science, mathematics and statistics, and a variety of disciplines including physics, chemistry, medicine and linguistics. It applies this knowledge in support of computation and information processing tasks relating to research, patient care and administration throughout NIH.

DCRT's past success in helping to establish computing as an indispensable tool of research and administration at NIH suggests that its plans should be for more of the same kinds of broadly based services and developmental activities.

Computing at NIH will never be static. The technology base has evolved through the accumulation of proven hardware and software systems and through the accumulation of knowledge and experience that has come from building these systems. One result is that DCRT staff has considerable confidence in attacking new projects. Another is that they are aware of the need to maintain compatability between new and old systems.

The scientific and mathematical base within DCRT is also solid, and division staff will continue their productive collaboration with other NIH scientists. Barring events outside NIH, there should, therefore, be considerable stability in the computing environment for users throughout NIH.

Factors Affecting the Evolution of DCRT and Computing at NIH. Three principal factors affect the future of computing at NIH and DCRT's service and research roles. These are:

· user response

· technological environment

· administrative environment.

User Response. Experience indicates that scientists and administrators at NIH will make use of existing services and facilities and that they will welcome new advances in computing that they perceive as advantageous to their work. Both the driving force and the limiting conditions for successful applications derive from how well users understand their own information processing needs and the ways of using computer technology effectively in their work. DCRT will therefore strive to keep NIH users aware of new information processing tools and techniques and to offer demonstrations, training courses, seminars and other assistance for both old and new users.

The Technological Environment. The dominant recent advance in digital electronics has been large scale integrated (LSI) circuitry. The resultant drop in cost of hardware components has a dramatic popular manifestation in the appearance of powerful electronic calculators, some costing less than five dollars. A counterpart is microprogramming permitted by LSI hardware, manifest

most widely as the complex single button functions available in more expensive calculators. There are even microcomputers of limited capacity and memory costing less than $100.

The major cost for many applications of computers has become peripheral equipment and of the time and expertise to plan, develop and test the programs, and the DCRT will probably devote most of its limited manpower to more complex hardware for advanced applications within the NIH laboratories.

It is clear, however, that many scientists and administrators will make increasing use of programmable calculators and that experience with these devices will provide an understanding of many computing concepts and an appreciation of the advantages of computer systems which maintain and operate upon data files.

The Administrative Environment. The steadily increasing use of computers in Federal agencies during the past two decades has generated perennial concern within the Federal establishment about costs and administrative review mechanisms. Since annual expenditures reported for "Total NIH Automatic Data Processing Operations" during the past five years extrapolate to an annual total of $100 million within five or six years, the concern of the General Services Administration, the Office of Management and Budget, DHEW and the PHS can be expected to heighten markedly. This concern has led in the past to efforts to standardize justification and procurement procedures for acquisition of new ADP equipment and the mechanisms that govern development of new applications for computers already in use. Unfortunately, some of the procedures are outdated and others are based on misconceptions about what is needed to create good computing systems and applications. Unless administrative procedures are kept flexible and responsive to new needs created by technological advances and to the particular requirements of NIH research and administration, computing at NIH could atrophy from immobility created by splints and casts designed to rectify weaknesses in other organizations.

How much effect administrative constraints outside of NIH have upon its computing capability will depend upon the extent to which they can be anticipated and influenced by the demonstrated success of NIH computing. Fortunately, NIH administrative mechanisms on the whole perform well and the widespread recognition of the high quality of computing at NIH is a strong support. If these factors can be enhanced, computing in DCRT and in NIH as a whole can be expected to continue its favorable evolution from the existing solid base.

The DCRT Itself

"The reports of the laboratory and branch chiefs speak for themselves." This single sentence was the perennial summary offered by Dr. Robert Berliner during his years as Scientific Director of the National Heart Institute to express his pride and confidence in the work of his staff. The work of the six branches and laboratories of the Division of Computer Research and Technology deserves no less an endorsement, but the division's activities are so diverse that an overview is needed to show how these activities relate to each other and to the work of NIH as a whole.

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All six branches and laboratories are involved in both collaborative service and research and development projects, but the balance of each type of responsibility differs. About two thirds of the staff, predominantly in the Comput Center and Data Management Branches, provide the wide variety of computing services. The four DCRT laboratories reach into all NIH Institutes, Divisions, Bureaus and Offices through consultation to NIH staff who need advice and assistance on their computing projects and through collaborative research and development projects. In addition, all six branches and laboratories carry on their own research and development projects to generate new techniques and theories applicable to biomedical research and its administrative support at NIH. Members of all labs and branches also teach computer technique courses and seminars for NIH staff as part of DCRT's Information and Education programs.

* The Computer Center Branch (CCB) designs, implements and maintains the central NIH computing utility, accessible day and night to users from more than a thousand registered terminals. During FY76, this utility logged almost a million interactive terminal sessions by its users and more than two million jobs done in its job stream. The center continues to be recognized by many other Federal agencies and by experts in the private sector as the most accessible, reliable computer facility in the Federal government and perhaps the entire country.

* The Data Management Branch (DMB) and the Laboratory of Statistical and Mathematical Methodology (LSMM) made this central computing power useful for the specific tasks of scores of NIH scientific and administrative users. LSMM and DMB have built and acquired a powerful library of statistical, mathematical and data management software tools to meet NIH needs. Equally important, they provide consultation and advice to users and develop new programs for them when the existing packages are not appropriate for particular tasks.

* The Computer Systems Laboratory (CSL) uses its engineering expertise to design and develop computer systems to handle tasks for which the NIH central computing utility is not the appropriate resource. Many of its products and ideas have been copied and adopted by other organizations. CSL serves as consultant to other groups at NIH in the procurement of small computers.

* The Laboratory of Applied Studies (LAS) and the Physical Sciences Laboratory (PSL) carry on collaborative projects with scientists in the NIH institutes. They also serve as consultants on the use of mathematical theory and computing methods in biochemistry, biophysics, and clinical medicine.

Highlights of Activities

DCRT's activities can be viewed, for convenience, as being divided between the software development spectrum and the application spectrum. Both are involved in the work of all the branches and labs.

The Software Development Spectrum. Good computing depends upon good programming; and this, in turn, depends upon specialized human knowledge and skills. To perform hundreds of thousands of separate small steps in an information processing task, the computer (the hardware) must be directed by programs (the software) developed by creative and talented people who can apply the principles of

computer science and software engineering to real world tasks. The DCRT is recognized by knowledgeable computer scientists and computer industry professionals both for the breadth and reliability of its services and for its innovative software developments.

The DCRT software spectrum includes several types of programs: those that control computer systems and those designed to facilitate broad categories of information processing, such as text editing, file building and query, statistics, equation solving, curve fitting and graphics. DCRT also designs many specific programs, large and small, to meet particular needs at NIH. These range from laboratory process control and complex mathematical models to programs that keep track of and report upon such administrative details as grants, contracts and parking permits.

DCRT labs and branches have developed or contributed significantly to several major pieces of software that have been widely accepted not only at NIH but elsewhere among computer users. These include SPOUT, Shared Spool, WYLBUR, Omnigraph, IPP, RMAG, Modelaide and MLAB. Others, equally noteworthy, are less likely to be exported because they were written specifically for use by DCRT in its support of computing at NIH; for example, the DCRT Project Accounting System and the Data Management Branch's program generators.

One major systems software project of FY76 is mentioned in a single passing sentence in the Computer Center Branch summary later in this report. This involves the conversion to a new IBM System 370 operating system. "The Bridge, used during this conversion, was designed to achieve the transition without disrupting service. It provides NIH computer center users with a combined system during the conversion rather than confronting them with a sudden change from the old MVT to the new MVS operating system. Like many NIH systems programs, the measure of this program's success lies in the fact that users remained virtually unaware of its existence.

The increasing use of minicomputers, microcomputers and programmable calculators in NIH laboratories and clinics presents new software development challenges to DCRT staff. Programming skill must be joined with engineering expertise to interface these small computers to a great variety of electronic machinery: laboratory instruments, devices used to monitor the vital functions of patients in intensive care units, machines that read coded labels on books or even to larger computers that enhance the capabilities of the small computers. Many such products and ideas of the Computer Systems Laboratory have been exported and emulated outside of NIH.

For computer programming to be effective, the right questions must be asked and the right numerical techniques must be used. The DCRT laboratories back up their programming skills with mathematical and statistical expertise and with substantive knowledge of physics, chemistry and clinical medicine that enables staff to insure that software programming is directed toward appropriate scientific questions.

The Application Spectrum. Part of DCRT's charge in 1964 was "to stimulate the introduction of Automatic Data Processing methodology into on-going programs" at NIH; in other words not just to create computer systems but to make them

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useful in meeting the particular needs of biomedical research and administration. By FY76, computing had become an integral activity in every part of NIH--in every Institute, Bureau and Division; in laboratories, clinics and administrative offices.

This success is due in large measure to DCRT's dual approach to its task. The Division sees its interrelating functions as:

* providing distributed computing capacity, and

* helping computer users to become knowledgeable and self-reliant.

In some instances DCRT functions primarily as consultant, as it has done in helping the Clinical Center choose and install its new clinical laboratory system and its new hospital information system. DCRT could maintain this limited role because the Clinical Center's Office of Clinical and Management Systems has its own computing expertise.

In other applications, DCRT is much more extensively involved. In setting up the NHLI Surgical Intensive Care Unit, for example, DCRT staff had to have full understanding of the physiologic variables to be monitored in order to assume responsibility for choosing hardware and software that would best serve the purpose.

In still others, for example, DCRT's work with the Clinical Center's Nuclear Medicine Branch, there is a collaborative effort involving computing and scientific expertise in both organizations and scientific partnership with other institutes as well. The result is the very sort of multidisciplinary hardware/software/mathematical/scientific synergism envisioned by the 1963 NIH report calling for formation of the DCRT to put the great potential of computers to work at NIH.

DCRT's multidisciplinary collaboration extends beyond the NIH. For example, DCRT has worked jointly with the NHLI Laboratory of Chemistry, the Environmental Protection Agency, the Brookhaven National Laboratories and several university research groups on development of chemical information systems. Other examples of DCRT's collaboration in multiagency, multidisciplinary projects appear in the Individual Research Project reports for FY76.

In administrative management applications also, the degree of DCRT's involvement adapts to the circumstances of each project. In some instances, such as development of the Combined NIH Mailing List System for DRG, the DRS Support System and the NCI Computerized Grants Information System, DCRT does the design and programming. In others, such as the NIH Materiel Management System, DCRT provides consultation on work done by outside contractors selected by the NIH B/I/D office.

The Underlying NIH Philosophy. The prevalence and level of excellence of computer applications at NIH, achieved in a relatively short span of years, reflects NIH's underlying philosophy as manifest in the DCRT and NIH development of computational resources:

- that primary emphasis should be given to creating a sound scientific and technical base

- that adequate facilities and training programs must be included

- that decision-making authority is to be delegated to appropriate levels of scientific and administrative expertise.

It is clear that these basic prinicples have served the NIH as well in the development of information processing technology as in the support and conduct of biomedical research.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT

2. OFFICE OF SCIENTIFIC AND
   TECHNICAL COMMUNICATIONS

3. William C. Mohler, M.D.
   Chief

I. SUMMARY

Function

The DCRT Office of Scientific and Technical Communications, under the direction
of the Associate Director of the Division, is responsible for three areas of
activity:

' The DCRT Library

' the Division's Information Office

. a program of mathematics and computer technology applied to biomedical image
  processing and decision analysis.

Highlights of the Year's Activities

The DCRT Library. This specialized library maintains a collection of publica-
tions in computer science and mathematics and related areas of engineering,
information science and management. Its bibliographic and reference services
support the DCRT staff directly, provide a resource for the rest of NIH and
function as an active part of a local network of special libraries sharing
resources in the Washington area.

In FY76, over 100 new users registered with the library. Circulation of books
and monographs was about a third greater than in FY75, partly as a result of
changes in loan periods and staff efforts to get books returned promptly for
the use of those on waiting lists. Membership in the 65 member Washington
Area Interlibrary Users Association (IUA) increased interlibrary loan activity
during the last half of the year by more than 80%.

Despite more than 200 additions, the monograph collection remained at about
3500 cataloged monographs, because the DCRT Library Committee and other DCRT
staff responded to the librarian's call for help in reviewing and weeding the
collection. Part time help under the NIH "Stay-in-School" program made it
possible to inventory all journal holdings and 90% of the books, and to update
the catalog and shelf list.

Plans for the coming year include more work on inventory, collection review,
review of circulation performance and some modest changes in work area layout,
all to provide maximum benefit to users within DCRT space and staff limitations.
A trial participation in the Federal Library Committee/Ohio College Library
Center (FLC/OCLC) on-line cataloguing service should benefit interlibrary loan
service and acquisitions as well as cataloguing. Modifications to our

existing automated circulation records system may be useful; we have been surveying the experience of others to evaluate potential benefits and costs of a new or revised system.

The Information Office. During the first half of FY76, the entire staff, the Information Officer and her part time assistant, retired to full-time motherhood. Recruitment benefitted from, but was also delayed by, the successful NIH effort to secure approval from DHEW for Information Officer positions at the B/I/D level. The new Information Officer came on board at the end of the fiscal year empowered to handle the full range of duties traditionally associated with that title at NIH.

The Information Office is responsible for a diverse set of tasks. In some of its major activities during FY76, the Office

* revised and reissued the DCRT "Services and Facilities" brochure
* redesigned the DCRT public information booklet "Tools for the Advancement of Medicine"
* planned and participated in the Second NIH Open House as part of the NIH bicentennial effort
* prepared reports on the effect of the Freedom of Information Act on DCRT activities
* coordinated preparation of the Annual Report.

During the coming year, the Information Office plans to develop new ways to inform various "publics" within NIH about computer applications of benefit to biomedical research and administration. It will also increase its efforts to make both the scientific and the general public more familiar with DCRT's work and important accomplishments by DCRT and NIH staff in various areas involving computer research and technology. Two projects begun during FY76 will contribute to this effort. The first was a redesign of the Division's annual report to make it more informative and readable. The second grew out of recognition of several DCRT staff members of a need for a compact annual review of highlights of the Division's activities. Initially this was conceived as a document directed primarily toward NIH users or potential users of DCRT's technical services. Later, the concept was expanded to include distribution to technical visitors, DCRT and other interested NIH staff and some categories of lay visitors. During the last half of the year, a professional consultant worked with DCRT staff on both these projects.

Biomedical Image Processing and Decision Analysis. These activities encompassed three areas:

* research
* advice and consultation
* presentations at professional and educational meetings.

Research. Two of the research projects extended previous work using computers to characterize microscopic images of cells by objective measures and to extract reliable criteria for discriminating among normal and malignant cell t

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Most previous work in this field was done on cell smears and several machines are now available to perform differential counts on white blood cells. Research on histological sections is more difficult for a number of theoretical and technical reasons. Progress has been limited by the unavailability of suitable clinical biopsy material and of suitable microscope/digitizing facilities to create well digitized images of individual cells.

A third project involved applications of a three part computer system (PEEP-DECIDE-GRAPH) developed to facilitate analysis of digitized microscopic images and medical decision making. The basic system was created several years ago and is an excellent example of a growing number of interactive systems designed to put mathematical tools literally at the fingertips of scientists. Analysis of digitized microscopic images is a two dimensional case of some more general "n dimensional" mathematical problems that involve identifying patterns among data and processing them to extract useful information.

<u>Advice and Consultation</u>. These activities included work with the following groups:

* the Division of Cancer Biology and Diagnosis of the National Cancer Institute as a member of the Committee for Cytology Automation and the Diagnostic Radiology Advisory Committee

* the NCI Breast Cancer Task Force, the National Heart and Lung Institute, RANN and the Division of Computing Science of the National Science Foundation, and the Department of Labor in the area of cluster analysis

* membership in the U.S./Japan Cancer Cooperative Research Program on Cytology, the U.S./Japan Biomedical Image Processing Seminar and the NSF Inter-Agency Panel on Medical Physics whose emphasis in FY76 was on ultrasound

* work on the IEEE Machine Pattern Analysis Group and its subcommittees on Image Processing and Scene Analysis, Data Bases and Biomedical Image Processing.

<u>Presentations and Papers</u>. The numerous presentations and papers given by J.M.S. Prewitt covered many of the topics (see list which follows). During FY76, Mrs. Prewitt was also a national visiting lecturer for the Society for Industrial and Applied Mathematics (SIAM) on topics relating to image processing and decision analysis. She is also an Associate Editor of "Computer Graphics and Image Processing."

III. Presentations and Papers

Judith M.S. Prewitt

Computer Logic for Automated Cell Identification and Specimen Classification. Second U.S./Japan Cooperative Cancer Research Program on Cytology, San Francisco, California, June 1975.

Decision Theoretic Approaches to White Cell Differentiation. Proceedings IFIP Working Conference on "Decision Making and Medical Care: Can Information Science Help," Dijon, France, May 1976. *

Prospective Medical Advances in Computerized Tomography. Symposium on the Basicranium, Bethesda, Maryland, June 1975. *

Current and Future Research in Reconstructive Techniques in Medicine. Identification of New Areas of Application. American Physical Society Meeting, Washington, D.C., April 1975. *

New Vistas in Medical Reconstruction Imagery. U.S./Japan Conference on Bio-Medical Picture Processing, Pasadena, California, October 1976. *

New Vistas in Medical Reconstruction Imaging. Image Processing Institute of the University of Southern California, May 1975.

NCI/DCBD Research Program on Computerized Reconstruction Tomography in Diagnostic Radiology and Nuclear Medicine. San Juan Workshop on Reconstruction Tomography in Diagnostic Radiology and Nuclear Medicine, April 1975.

Diagnostic Radiology Studies - New Research Projects. DCAD/NCI Diagnostic Overview Meeting, Columbia, Maryland, October 1975. *

Scene Analysis. Engineering Foundation Conference on Cytology Automation, Asilomar, California, July 1975.

Pattern Analysis as an Investigative Tool in Microscopy. IEEE-ACM Computer Graphics Pattern Recognition and Data Structure Conference. Los Angeles, California, May 1975.

A Computing Mileu for a Class of Biomedical Pattern Information Processing Tasks. IEEE-ACM Computer Graphics Pattern Recognition and Data Structure Conference, Los Angeles, California, May 1975.

Making the Computer Easier to Use in Biomedical Sciences. CompCon, Washington, D.C., September 1975.

Principles and Applications of Optical Data Pattern Recognition in Microscopy. United States Environmental Protective Agency, Corvallis, Oregon, June 1975.

Near Future Prospects for Biomedical Image Processing. NSF Conference on Near Future Prospects for Image Processing, Silver Spring, Maryland, May 1975.

Problems in Biomedical Image Processing. University of Florida, Gainesville.
Florida, November 1975.

Two Decades of Medical Image Processing. Optical Society of America, Pacific
Grove, California, February 1976. *

Ultrasonic Tissue Signature Library. International Conference on Ultrasound
in Medicine, Gaithersburg, Maryland, May 1975. *

*Printed Papers

PERIOD COVERED

July 1, 1975 – June 30, 1976

TITLE OF PROJECT (80 characters or less)

NCI Bladder Cancer Image Processing

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Judith M.S. Prewitt

COOPERATING UNITS (if any)

St. Vincent Hospital, Worcester, Mass.

Jet Propulsion Laboratory, Pasadena, Calif.

LAB/BRANCH
Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION
DCRT/NIH

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.30	0.20	0.10

SUMMARY OF WORK (200 words or less – underline keywords)

The long range goal of this project is to quantitatively characterize the epithelium of human urinary bladder from scanned digitized images of stained sections using digital computers and to develop a data-directed taxonomy for the range of tissues from normal to invasive carcinoma.

Tissue sections were prepared on microscopic slides at St. Vincent Hospital, Worcester, Mass. and stained with hematoxylin. They were scanned at the Jet Propulsion Laboratory, Pasadena, Calif. so that the resulting images were at 630X, sampled at half micron intervals and rendered in 256 linear gray levels. The material was routine clinical preparations of variable and sometimes mediocre quality. The absorption peak for the tissue sections was determined to be at 570NM and all scans were made at both this wave length and in white light. In one experiment with tissue sections stained with gallocyanin chromalum, the response in the entire visible range was assessed.

The PEEP-DECIDE-GRAPH system was used to analyze the digitized images. (In fact, the project was the impetus for implementing that system, which is discussed in a separate project report). All of the object extraction methods

PHS-6040

were applied to digitized images of tissue sections. They met with varying degrees of success and depending on the quality of the tissue sections, one or another method may be necessary.

Two morphologically distinct tissue sections were chosen for in-depth study. Both yielded to thresholding for obtaining nuclear images. The entire armamentarium of PEEP features was extracted on approximately 20 nuclei from each tissue. Linear and quadratic discriminant analysis were used to learn each tissue section as a category. Specimens from each tissue were then classified with the following result of demonstrated internal consistency: nuclei in one tissue type were overwhelmingly more like each other than like cell nuclei from other tissue types.

The data directed classification of tissue sections might well be an improvement over current subjective and often dubious decisions. The difficulty of the undertaking should not be under emphasized. Classification using algorithms may lead to greater objectivity, public verifiability, and greater consistency. There is always the opportunity for discovering new significant differences in optical properties between papillomas and papillary carcinomas using the digital computer.

At the present time the project is inactive but it may be reactivated during the next fiscal year, if suitable tissue section material becomes available.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 CT 00028-01

PERIOD COVERED
July 1, 1975 – June 30, 1976

TITLE OF PROJECT (80 characters or less)

Characterization of Cells from Breast Aspirates.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

COOPERATING UNITS (if any)

Academic Hospital, Uppsala, Sweden

LAB/BRANCH
Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION
DCRT/NIH

TOTAL MANYEARS: 0.35	PROFESSIONAL: 0.25	OTHER: 0.10

SUMMARY OF WORK (200 words or less - underline keywords)

The long range objective of this project is to characterize images of cells from human breast aspiration biopsies, and to distinguish malignant from benign cells. Aspiration biopsy is used widely in Europe but not in the United States.

Biopsy material was prepared at the Department of Clinical Cytology, Academic Hospital, Uppsala, Sweden, stained with Papanicolau stain and scanned there, digitized and recorded on magnetic tape. The Uppsala scanning microscope has 7/10 micron square aperture and has a moving stage and records 256 gray levels. Using the PEEP system, cell images were displayed and thresholded. This generated objects which were subjected to feature extraction using the PEEP/DECIDE system. Eighteen numeric characterizing features were extracted for each of 100 cell nuclei in five cell categories. Examples of these features are area, average brightness, average chord, entropy, kurtosis and skewness of the optical density histogram, density, variation in brightness, variation in chord length and variation in diameter.

Each of four categories of benign cells was distinguished from the category of malignant cells. Using quadratic discriminations, combinations of as few as

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Characterization of Cells from Breast Aspirates.

four features and in some cases a single feature allowed perfect discrimination between pairs of cell categories. Useful features included skewness of the optical density histogram, nuclear area, length of major axis, density and entropy.

The practical significance of this research lies largely to developments in the automation of cytologic examinations. The project will be continued both in the United States and Sweden using more carefully scanned cells prepared with gallocyanin chromalum.

PERIOD COVERED

TITLE OF PROJECT (80 characters or less)

Other Applications of PEEP/DECIDE/GRAPH

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Judith M.S. Prewitt

Dr. R. Brooks, National Institute of Neurological and Communicative Disorders

Dr. K. Kent, National Heart and Lung Institute

COOPERATING UNITS (if any)

St. Elizabeth's Hospital, Washington DC
Princeton University, Princeton, N.J. Dept. of EE

LAB/BRANCH
Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION
DCRT/NIH

TOTAL MANYEARS: .55	PROFESSIONAL: 0.05	OTHER: 0.50

SUMMARY OF WORK (200 words or less - underline keywords)

PEEP/DECIDE/GRAPH is an interactive programming system written in SAIL, the Stanford Artificial Intelligence Language, and operating on the DCRT PDP-10 computer. PEEP is designed for picture processing applications, DECIDE is intended for algorithmic decision making and exploratory data analysis, and GRAPH has capabilities for two and three dimensional graphics. The system was originally written for the NCI Bladder Cancer Image Processing Project but is of wide utility. In the PEEP system and appendages to it, objects can be obtained from optical density histograms. This option is available in global and local form. Derivatives, Laplacians and Hueckel operators can be applied. A large library of feature extraction algorithms has been built. These features encompass numeric descriptions of size, shape, content, contrast, comparison and orientation. Examples of such features are area, average brightness, diameter, average chord, entropy, kurtosis and skewness of the optical density histogram, integrated optical density, variation in brightness, variation in chord length, variation in diameter, Fourier coefficients of a boundary, bending energy, medial axis transforms, major axis and minor axis.

DECIDE enables the performance of parametric and non-parametric recognition of

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objects. Linear and quadratic discriminant analysis form the basis for para-
metric recognition. Coefficients of the best discriminant function can be
learned from exemplary objects using a learn command. New test objects can
be classified into a learned category using the classify command. The user
has control over various parameters of the learning process. For example,
likelihood maximizing discriminant functions can be developed. Non-parametric
recognition is performed by the cluster command. Again, many variations of
data normalization, cluster merger strategy and cluster type emphasis are
available.

GRAPH allows the user to create and display graphic structures in two and
three dimensions and to use different vantage points for viewing them.

In conjunction with Dr. W. Shoemaker at St. Elizabeth's Hospital, morphometric
study of synapses of mammalian central nervous systems was undertaken. PEEP
was applied to the interactive extraction of neuronal synapse images appearing
in specially prepared electron micrographs. Ethanolic phospho-tungstic acid
was used to selectively stain synapses. The neuronal synapses were extracted
by iterative attempts at thresholding. This is the first time such an effort
has succeeded. The project was very expensive and no further work is contem-
plated at the present time.

In conjunction with Dr. R. Brooks at the National Institute of Neurological
and Communicative Disorders and Stroke, PEEP was used to obtain and manipulate
EMI two dimensional cross sectional reconstructions of the human head. Special
data conversion programs were written to format data so that PEEP could be used.
It is envisioned that one early application will be image subtraction.

In collaboration with Dr. K. Kent at the National Heart and Lung Institute, a
new project was started in order to make use of the decision making capabilities
of DECIDE. An on-line expandable data retrieval system was designed for the
purpose of compiling data on the natural history of patients with coronary
artery disease. Data on 200 to 300 patients over a period of two years will
be collected and entered by means of a special questionnaire. A general pur-
pose input program for composing questionnaires leading to data structures
compatible with DECIDE was written. Decision making logic will be developed
so that a prospective diagnostic scheme can be obtained. From time to time
graphic display is necessary. This project is similar but more elaborate than
another National Heart and Lung Institute collaborative program designed to
study pre and post-operative factors indicative of surgical risk.

In collaboration with Dr. T. Pavlidis at the Department of Electrical Engineer-
ing of Princeton University, a project was conducted to apply linear polygonal
segmentation to the nuclear and cell boundaries of normal human leukocyte
images. The segmentation algorithm was improved. It is contemplated that a
grammar for cell and nuclear boundaries will be devised. Features of the poly-
gonal boundary approximation could then be used for characterization.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT

2. OFFICE OF ADP POLICY
    COORDINATION

3. Henry J. Juenemann
    Chief

I. SUMMARY

Function

The DCRT Office of ADP Policy Coordination, under the direction of the Assistant Director of the Division, has two closely related functions. It serves as:

* the focus for NIH-wide coordination of automatic data processing policy matters

* the central NIH point of contact with the Public Health Service, the Office of the Secretary of the Department of Health, Education and Welfare and other HEW agencies, the General Services Administration and the Office of Management and Budget on policy questions and NIH's participation in policy development.

Scope of Work

As Chief of this office, the Assistant Director provides advice and assistance about internal DCRT operations and coordinates DCRT's ADP policies and activities with those of other agencies. He advises the Director of NIH and the Director of DCRT on ADP policy matters, assists the NIH Division of Management Policy on policy and procurement questions relating to its responsibility for administrative computer applications, reviews and evaluates proposals from NIH B/I/D's for ADP and computing procurements and contracts, directs development of the annual ADP Plan, represents the NIH in PHS and DHEW policy formulation efforts, works with GSA and OMB staff on procurements, coordinates Interagency Agreements with Federal agencies that use DCRT facilities, and answers inquiries from NIH scientists and administrators who are confused by the whole process.

Highlights of the Year's Activities

The "highlights" of FY76 began with the end of protracted negotiations for an upgrade of the DCRT Computer Center's 370 system. The procurement action begun in 1974 had escalated to involve the OMB in addition to the GSA. Final resolution involved the Director of NIH, two Assistant Secretaries and the Secretary of DHEW. An interim upgrade was allowed.

Another time consuming activity was working through a complaint about the contract awarded for the new editing display NIH 5200 terminals. This involved the GAO, PHS and DHEW and was resolved by an NIH review under the aegis of the

Associate Director for Administration and by the development of a successor request for proposal.

During FY76, as in each year since 1972, a major undertaking of this office was providing technical and management leadership in development of NIH's annual ADP Plan. This is a management process which yields a two year projection for ADP equipment, manpower and ADP support contracts for all components of NIH. This planning process creates an orderly opportunity to take stock of problems, goals and accomplishments. The FY76 plan reflected a total NIH ADP level of $35 million. To reduce the administrative burden of meeting numerous separate reporting requirements, this office attempts to integrate GSA and OMB reporting requirements into the NIH ADP plan.

In its NIH policy coordination role, this office reviews all NIH proposals for contracts or procurement actions involving ADP equipment, services or programming support as they are cleared through the office prior to being executed. This provides a continuous opportunity to alert program or contract officials to opportunities to avoid duplications, reduce costs and avoid difficulties with higher echelons.

Fortunately, most procurements and contracts go smoothly. During the year this office consulted on or reviewed 218 proposals from the B/I/D's and many more from within DCRT. They ranged in value up to $1.5 million. Most proposals coming to the office are processed promptly, with required GSA, PHS or OS/DHEW processing steps expedited. Coexistence of this office's clearance role with its internal DCRT role provides a unique opportunity. Sometimes, as plans and proposals from other NIH components are reviewed, apparent technical deficiencies are suspected. In such cases, this office can, so to speak, don its internal technical hat and arrange for whatever DCRT technical expertise is needed to resolve the deficiencies and help to improve the substance of the plans and proposals.

Perhaps the most notable achievement in FY76 was arrangement for and completion of an interagency agreement by which DCRT gained 17 personnel slots. These were transferred from the Bureau of Labor Statistics to DCRT in return for DCRT's agreement to provide statistically oriented computational support to the BLS.

Future Plans

ADP policies and requirements are becoming increasingly complex as OMB, GSA, DHEW and PHS become more and more involved in ADP policy development and management. As a result, the DCRT Office of ADP Policy Coordination must expect to spend an ever-increasing percentage of its available manhours in attempting to guide policy development in productive directions and in coping with the growing load of paper work. The office will continue to work to spare large numbers of NIH research and research support staff members the task of becoming expert in the many nuances of ADP-related regulations.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

2. <u>PHYSICAL SCIENCES LABORATORY</u>

1. <u>DCRT</u>

3. <u>George Weiss</u>
   Chief

I. SUMMARY

<u>Function</u>

The Physical Sciences Laboratory has three principal functions:

- to carry out research in the physical sciences in order to understand biological phenomena in terms of physics and chemistry

- to develop the theory and practical instrumentation for biomedical experiments, and in particular to relate these to the capabilities of modern computer technology

- to provide consulting services to other scientists at NIH in physics, theoretical chemistry, and several fields in applied mathematics.

The staff of the Physical Sciences Laboratory consists of six professionals who work in the areas of general biophysics, nuclear magnetic resonance, applications of light scattering techniques in biomedical experiments, the physical chemistry of polyelectrolytes and problems in applied mathematics.

<u>Scope of Work</u>

The Physical Sciences Laboratory has six continuing research projects in addition to its consulting services. These projects involve collaborative research with approximately ten other investigators both on and off campus. Two sets of investigators off-campus are carrying out experimental work in order to verify theoretical findings by members of PSL and to apply the theory to biological systems.

<u>Highlights of the Year's Activities</u>

<u>Role of Physical Forces in Biological Phenomena</u>. One of PSL's continuing project is development of theories of electrodynamic and electrostatic forces particularly as they apply to systems of biological interest. Present experiments with Dr. R. P. Rand of Brock University (Canada) use the theory to measure forces between phospholipid bilayer membranes by x-ray scattering.

These measurements are the first ever to be made for this order of magnitude of forces, on organic material. Now that the basic technique has been proved useful, many further studies will be undertaken. Other experiments are being done by Dr. D. Gingell, Middlesex Medical School (London) on the interaction of red cells with each other and with artificial materials. These experiments confirm that long range electromagnetic forces are important in these interactions.

Cell Motility and Chemotaxis. Collaborative experiments are presently underway with Drs. L. Kohn and Y. Chang (LBP/NIAMDD) for delineation of factors influencing leukocyte migration. The relevant theory for those has been developed by Dr. Ralph J. Nossal. Dr. Nossal is also evaluating data on bacterial chemotaxis taken by Dr. S. Zigmond of Yale University, in order to determine parameters to be used in a random walk theory recently developed in this laboratory.

Theory of Biochemical Separation Techniques. A technique for accelerating equilibrium sedimentation experiments has been developed. The theoretical improvement possible with this technique is of the order of 5 or 6, which would permit planning of presently impossible experiments with degradable proteins. Full realization of the theoretical acceleration is not yet possible because experimental error is considerably magnified by the technique. In the coming year we hope to use various smoothing techniques to suppress the noise.

II. PSL PROJECTS AND ACTIVITIES FY 76

Theory of Biochemical Separation Techniques. George H. Weiss, PSL, in collaboration with Dr. D. A. Yphantis, University of Connecticut. This project develops mathematical theory for the planning and interpretation of experiments with such techniques as chromatography, electrophoresis, and ultracentrifugation.

The Role of Electrostatic Forces in the Organization and Properties of Macromolecular Systems. Stephen L. Brenner, PSL, V. A. Parsegian, PSL. This project studies the role of electrostatic forces in determining the mutual arrangement and interaction of macromolecules in aqueous salt solutions.

Theory and Application of Nuclear Magnetic Resonance. James A. Ferretti, PSL. New techniques for carrying out NMR experiments are devised in this project together with new numerical methods for processing data from this type of experiment.

Correlation Function Spectroscopy/Laser Light Scattering. Ralph J. Nossal, PSL, Stephen L. Brenner, PSL. A laser inelastic light scattering spectrometer has been built. It will be used to measure parameters of cell motility and cytoplasmic transport. Related theoretical work is required and is being developed.

Cell Motility and Chemotaxes. Ralph J. Nossal, PSL, Stephen L. Brenner, PSL, and George H. Weiss, PSL. This project develops methodology for the interpretation of experiments related to cell locomotion and chemotaxis.

Theory and Measurement of Intermolecular Forces. V. A. Parsegian, PSL, George H. Weiss, PSL, James E. Kiefer, PSL. The object of these studies is to develop the theory of electrodynamic forces in biological media, and to develop experimental methods for measuring these forces.

Studies in Mathematics and Statistics. George H. Weiss, PSL, in collaboration with D. G. Hoel, NIEHS. Several studies are included in this study, which relate mainly to stochastic problems. At present these studies include the characterization of polymer configurations in probabilistic terms, the kinetics of emulsion polymerization, and the comparison of stochastic and deterministic theories of chemical reactions.

Consulting Services. George H. Weiss, PSL, Ralph J. Nossal, PSL, James E. Kiefer, PSL. Members of the PSL give consulting assistance to other scientists at NIH and elsewhere, in the areas of the physical sciences and applied mathematics.

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Weiss, G. H., Dishon, M.: A note on the kinetics of emulsion polymeriza J. Chem. Soc. (to appear).

Weiss, G. H., Rodbard, D.:   Measures of resolution for multicomponent systems in one and two dimensions with application to pore gradient electrophoresis. Separation Science (to appear).

PERIOD COVERED

July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Theory of Biochemical Separation Techniques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. H. Weiss   Chief, Physical Sci. Lab.   PSL,DCRT
     D. A. Yphantis   Professor of Biology
                         University of Connecticut
     R. Shinnar   Professor of Chemistry
                         CUNY
     M. Dishon   Research Fellow, NASA

COOPERATING UNITS (if any)

None

LAB/BRANCH   Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION   DCRT, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0.0

SUMMARY OF WORK (200 words or less - underline keywords)

This project is directed towards applying mathematical techniques to experimental methods commonly used for the separation of biochemical species such as electrophoresis or centrifugation. A topic of current interest is the develop-ment of a method for decreasing the experimental time used in sedimentation equilibrium experiments. A nonlinear transformation is being investigated but the surpression of noise is a major problem. Another phenomenon being investigated is the appearance of double peaks in dynamic isoelectric focussing. We are presently calculating solutions to equations which have the property of producing double peaks due to a nonlinear gradient.

In this project we have developed a technique for the acceleration of sedimentation equilibrium experiments. The method requires the use of an Aitken transformation of the data, which in turn requires precise optics in order to minimize noise. At the present time the technique shows considerable theoretical promise with the potential of reducing experiments to one quarter to one half their present duration. Measurement noise continues to be a limiting factor. Since the Aitken transformation is nonlinear the usual linear analysis of noise effects does not work very well. Numerical experiments suggest that the nonlinearities induce considerable changes in the distribution of the output noise. We are presently looking into the possibility of using a smoothing technique based on regularization. If this method proves useful it will be applied to other problems in the area of biochemical separation.

We have developed equations for the effects of altering plug shape in zonal centrifugation in order to minimize the number of cells that are lost to the wall in cell separation. We have considered the possibility of reducing the plug size and the effects of rotating the plug around an axis through the center of the centrifuge cell, showing that the wall loss will vary with the angle of rotation. Dr. Thomas Pretlow of the University of Alabama Medical School, who proposed the problem, will carry out experiments to either verify this prediction or show that other causes of cell loss are significant.

We have completed a study of resolution in biochemical separation procedures in one and two dimensions. In one dimension the resolution of two Gaussian peaks was considered, without making the usual assumptions that the mass and bandwidths are equal. Our study enables an investigator to delineate the effects of these parameters on the customary measure of resolution. Furthermore we have proposed several possible measures of resolution for two-dimensional separation methods with particular application to pore gel electrophoresis. We have shown that several plausible generalizations of the resolution criterion give similar results provided that some provision is made to limit the contribution to resolution made by points that are very far apart.

A current project is to find an explanation for double peaked curves of concentration that appear in dynamic isoelectric focussing experiments. We have proposed as an explanation of this phenomenon, a nonlinear gradient, rather than the linear gradient required by theory. Calculations are presently being made that support the proposed explanation.

Keyword Descriptors: electrophoresis, ultracentrifugation, resolution

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Publications:

Correia, J. J., Johnson, M. L., Weiss, G. H., Yphantis, D. A.:
Numerical study of the Johnston-Ogston effect in two component systems.
Biophysical Systems (to appear).

Weiss, G. H., Rodbard, D.: Measures of resolution for multicomponent
systems in one and two dimensions with application to pore gradient
electrophoresis. Separation Science (to appear).

Shinnar, R., Weiss, G. H.: A note on the resolution of two Gaussian
peaks. Separation Science (to appear).

TITLE OF PROJECT (80 characters or less)

Cell Motility and Chemotaxis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Ralph Nossal, Research Physicist   PSL,DCRT
Other: George H. Weiss, Chief   PSL,DCRT
         Stephen L. Brenner, Staff Fellow   PSL,DCRT

COOPERATING UNITS (if any)

Leonard D. Kohn, M.D.   Laboratory of Biochemical Pharmacology, NIAMDD
Yao T. Chang, M. D.   Laboratory of Biochemical Pharmacology, NIAMDD
Sally H. Zigmond   Section of Cell Biology, Yale Univ. Med. School

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.9	0.7	0.2

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been undertaken to study various aspects of cell locomotion and chemotaxis. A mathematical theory has been devised to relate chemotropism indices to the characteristic random walks of individual cells. Analytical expressions to quantitate capillary migration (MIF') assays have been derived. New procedures for measuring macroscopic coefficients of cell migration are being developed.

PHS-6040
(12-75)

Cell Motility and Chemotaxis

This study pertains to phenomena relating to cell locomotion and chemotaxis. Recent emphasis has been on examining immunologic aspects of leukocyte migration. One result is a mathematical theory for interpreting capillary migration assays for cellular immune sensitivity ('MIF' tests). Also, an analytic theory has been developed to relate the chemotactic response of neutrophil populations to parameters characterizing the stochastic movements of individual cells.

Collaborative experiments regarding analyses of leukocyte migration assays have been performed with Drs. L. D. Kohn and Y. T. Chang (LBP/NIAMDD). These involve the preparation of leukocyte derived migration inhibition factors, and subsequent study of changes they induce in the properties of migrating cells. Specialized techniques have been developed for this purpose, an example of which is a scheme in which occupation number fluctuations are analyzed to determine mobility coefficients of migrating cells.

Data for chemotaxis studies have been provided by Dr. S. H. Zigmond (Yale University), with whom a collaboration has been initiated.

Continuation of this research is anticipated. For example, an extensive analysis of factors which influence the design of number fluctuation experiments currently is in progress.

Publications:

Nossal, R., and Chang, Y. T.: A Procedure for Determining Mobility Parameters for Cells Moving Along Surfaces. J. Mechanochem. Cell Mot. (in press).

Nossal, R. ; Directed Cell Locomotion Arising From Strongly Biased Turn Angles. Math. Biosci. (in press).

Nossal, R.: Mathematical Analysis of a Capillary Migration Assay for Cellular Immune Sensitivity. J. Theoret. Biol. (in press).

Nossal, R.: Factors Affecting the Reliability of Capillar MIF (Migration Inhibition Factor) Assays. in Theoretical Immunology, ed. G. I. Bell, A. S. Perelson and G. H. Pimbley, Marcel Dekker, N.Y. (in press).

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Correlation Function Spectroscopy/Laser Light Scattering

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Ralph J. Nossal, Ph.D.   Research Physicist   PSL,DCRT
Other: Stephen L. Brenner, Ph.D.   Staff Fellow   PSL,DCRT

COOPERATING UNITS (if any)

H. Saroff, Ph.D., Laboratory of Biophysical Chemistry, NIAMDD
R. Gelman, Ph. D., Laboratory of Biochemistry, NIDR
D. Forman, Naval Medical Research Institute

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.3	0.2

SUMMARY OF WORK (200 words or less - underline keywords)

A laser inelastic light scattering spectrometer has been constructed. Experimental and theoretical studies have been performed in order to develop techniques for studying cell motility and cytoplasmic transport. Modifications of existing technology in order to study structures larger than the wavelength of light are in progress.

Correlation Function Spectroscopy/Laser Light Scattering

A principal objective of this project is to develop laser inelastic light scattering techniques for performing rapid and precise measurements on biological cells and macromolecules.   In principle, any process giving rise to refractive index fluctuations can be monitored.   For example, concentration fluctuations can be used to determine diffusion coefficients of macromolecules, rate constants of biomolecular reactions, or swimming speed distributions of motile microorganisms.

During the past year an inelastic light scattering spectrometer has been constructed, which currently is located in facilities made available to us by the Laboratory of Biophysical Chemistry, NIAMDD. A number of investigations have been initiated with the instrument, emphasis being on phenomena related to cytoplasmic transport and cell motility. Theoretical analyses have been performed in conjunction with the experimental studies. Various applications to structures larger than the wavelength of light are envisioned.

Future instrument development may involve design and construction of apparatus for detecting electrophoretic mobilities and also, instrumentation for performing fluorescence intensity fluctuation spectroscopy.   Also, we anticipate modifying the specially designed electronic correlation-function analyzer currently used for data acquisition and processing.

Keyword Descriptors: Laser light scattering, macromolecules, diffusion coefficients, correlation functions.

PERIOD COVERED

July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Consulting Services

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. H. Weiss, Chief, Physical Sciences Laboratory   PSL,DCRT
Other: R. J. Nossal, Physicist   PSL,DCRT

COOPERATING UNITS (if any)
William C. Caveness, Chief, Laboratory of Experimental Neurology, NINDS
Eugene T. Fischmann, Department of Cardiology, Howard University
David Forman, Research Physiologists, BD, NMRI
Rodney Brooks, Research Physicist, SN, NCI

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	0.0

SUMMARY OF WORK (200 words or less - underline keywords)

Members of the Physical Sciences Laboratory provide consulting services to scientists at N.I.H. in the areas of the physical sciences and applied mathematics. A continuing project is the planning of a study of head injured veterans of the Vietnam war to be carried out at a consortuim of hospitals. Some work has been done on the development of noise in the EMI scanner. A third project has been on the reduction of data from experiments in nerve regeneration.

PHS-6040
(12-75)

Consulting Services

In this project we have almost completed the analysis of survival data on German veterans of the First World War. The question of interest in this study is how the injury parameters affect life span. Our findings show that there are very few parameters that show any identifiable influence on life span. This work will be written up in the coming year.

At the request of Dr. Rodney Brooks, we developed a theory of noise that has application to the EMI scanner. The theory included expressions for the variance and correlations of noise at various points in the head, and the effects of different interpolation techniques on these statistical parameters.

Dr. Nossal has consulted with Dr. David Forman on analytic problems related to axonal transport and nerve regeneration. For example, a scheme has been devised to estimate the mean length of fibers which have regrown from a crushed nerve. This information is necessary for the evaluation of experiments which study factors influencing regeneration. Dr. Nossal has also assisted members of the Laboratory of Technical Development (NHLI) to develop noninvasive techniques for blood flow measurement based on light scattering.

Keyword Descriptors: Head injuries, life span, noise, EMI scanner, nerve regeneration.

Publications:

Weiss, G. H., Yeandle, S.: Distribution of response times in visual sense cells after weak stimuli. J. Theoret. Biol. 55, 519-528 (1975).

PERIOD COVERED

July 1, 1975 to June 30, 1976

TITLE OF ⌐. 'CCT (80 characters or less)

Studies in Mathematics and Statistics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. H. Weiss,	Chief, Phys. Sci. Lab.	PSL,DCRT
Other:	D. G. Hoel,	Chief, Biometry Branch	EBB,NIEHS
	M. Dishon	Research Fellow	NASA
	D. E. Blumenfeld	Lecturer, University College,	London
	R. J. Rubin	Senior Scientist	NBS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.25	0.25	0.0

SUMMARY OF WORK (200 words or less - underline keywords)

This project includes several unrelated studies which can be characterized as mathematical or statistical. The topics of present interest are: 1) the relation between deterministic and stochastic models of chemical reactions when there is an absorbing state; 2). the characterization of polymer dimensions in terms of the ordered spans of random walks; 3) the kinetics of emulsion polymerization.

Studies in Mathematics and Statistics

A considerable amount of work has been devoted to the comparison of solutions to equations that can be described by mass action laws or by birth and death equations. There are theorems to the effect that when the number of particles (or organisms) in such a system tend to infinity then the deterministic description contains all the information in the more detailed theory. However, there are systems for which this obviously cannot be so. We have studied the case, that can be described by the equations $A + B \to A + A$, $A \to B$ which, on a stochastic theory, must lead to an equilibrium state in which there are only B particles. The mass action analysis allows the possibility of an equilibrium state in which there may be A's. We have shown that the stochastic theory implies the existence of a quasi steady state that coincides with the deterministic steady state, and has an average lifetime that tends to infinity as the number of particles tends to infinity.

We have continued to work on a description of the dimensions of polymer chains in terms of the ordered spans of random walks. Most recently we have calculated properties of the dimensions of star molecules.

Another topic that has and is being studied is the kinetics of emulsion polymerization. We have developed a perturbation technique that is useful when the average number of free radicals per particle is small.

We have continued to investigate the properties of acoustic noise from highway traffic. In particular we have studied sampling techniques used for noise measurements and shown that they are robust with variations in the distributions of headway.

Keyword Descriptors: birth and death processes, polymer chains, random walks, emulsion polymerization, highway noise.

Publications:

Hoel, D. G., Sobel, M., Weiss, G.H.: Comparison of methods for choosing the best binomial population with delayed observations. J. Stat. Comp. and Simul. 3, 199-213 (1975).

Hoel, D. G., Sobel, M., Weiss, G. J.: A survey of adaptive sampling for clinical trials. Perspectives in Biometry 1, 2961 (1975).

Simon, R., Weiss, G. H.: A class of adaptive sampling schemes for selecting the better of two binomial populations. J. Stat. Comp. and Simul. 4, 37-47 (1975).

Hoel, D. G. Weiss, G. H.: A clinical trial design with a fixed maximum number of failures. Commun. in Statistics 4, 429-437 (1975).

Weiss, G. H., Dishon, M.: Application of a singular perturbation expansion to the solution of certain Fokker-Planck equations. J. Stat. Phys. 13, 145-155 (1975).

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Blumenfeld, D. E., Weiss, G. H.: Attenuation effects in the propagation of traffice noise. Transp. Res. 9, 103-106 (1975).

Blumenfeld, D. E., Weiss, G. H.: Effects of headway distributions on second order properties of traffic noise. J. Sound and Vib. 41, 93-102 (1975).

Weiss, G. H.: Asymptotic correction terms for the theory of the simple epidemic. Epidemiology, (SIAM, SIMS, Philadelphia) 144-150 (1975).

Weiss, G. H.: The two-state random walk. J. Stat. Phys. (to appear).

Weiss, G. H.: Rubin, R. J.: The theory of ordered spans of unrestricted random walks. J. Stat. Phys. (to appear).

Rubin, R. J., Mazur, J., Weiss, G. H.: Spans of polymer chains. Pure and Applied Chem. (to appear).

Weiss, G. H., Dishon, M.: A method for the evaluation of certain sums involving binomial coefficients. Fibonacci Quart. 14, 75-77 (1976).

Weiss, G. H., Dishon, M.: A note on the kinetics of emulsion polymerization. J. Chem. Soc. (to appear).

Oppenheim, I., Shuler, K. E., Weiss, G. H.: The Master Equation in Chemical Physics. (M.I.T. Press, Cambridge, Mass.) to appear.

PERIOD COVERED

July 1, 1975 to June 30, 1976

TITLE OF PROJECT (60 characters or less)

Theory and Application of Nuclear Magnetic Resonance Spectroscopy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: James A. Ferretti, Ph.D.   Research Chemist   PSL,DCRT
Other: E. D. Becker, Chief, Laboratory of Chemical Physics, LCP,NIAMDD
         L. K. Barden   CSL, DCRT
         R. R. Ernst, Professor, Laboratorium fur Physikalische Chemie,
             Eidgenossische Technische Hochochule, Zurich, Switzerland
         G. R. Marshall, Professor of Physiology, Department of Physiology
             and Biophysics, Washington University School of Medicine,
             St. Louis, Mo.

COOPERATING UNITS (if any)

NIAMDD

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	1.0	0.3

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to develop new methods in nuclear magnetic resonance spectroscopy and also to apply NMR to the study of small proteins. In particular, development of the correlation method of obtaining NMR spectra is of special interest. An experimental and theoretical study of interference effects in correlation spectroscopy has been undertaken. Saturation effects in correlation NMR are currently being studied. Investigations of the solution conformation of derivatives of Angiotensin and Bradykinin is in progress. Preliminary results show that marked changes in the conformation of Angiotensin derivatives occur with very little change in biological activity.

Interference Effects in NMR Correlation Spectroscopy

This investigation is concerned with a theoretical analysis and
experimental study of non-linear interference effects in NMR
correlation spectroscopy.   These non-linear effects are often observed
under conditions of optimum sensitivity in coupled spin systems, where
the required vf power levels cause partial saturation.   The origin of
these non-linear effects is analogous to that for pulse Fourier spectroscopy
and for stochastic resonance.   In correlation spectroscopy the interference
effects will strongly depend on the applied sweep rate used to excite
the various resonance transitions. We distinguish between transverse
interference and longitudinal interference effects.   In the case of
longitudinal interference the transverse components of magnetization
completely decay before the next resonance in sequence is excited although
longitudinal relaxation is negligible during passage through the entire
spectrum.   Transverse interference effects may be observed when the
transverse magnetization develops after passage through the resonance
region.   These criteria correspond to typical conditions which are used
in correlation spectroscopy.   Because these effects are observed in
spin coupled systems, the theoretical treatment requires a density
matrix description of the time development of the spin system.   The
phases and intensities of the various transitions are then calculated
for various values of the effective flip angle, sweep rate, and population
numbers appropriate to the particular molecule under investigation.   For
the transverse interference situation in a coupled two spin system,
maximum distortion is predicted and also experimentally observed to
occur for a sweep rate of twice the product of the chemical shift difference
with the spin coupling constant when the effective flip angle is ninety
degrees.   The distortion occurs in the first doublet which is excited by
the rf power.   Where small effective slip angle is employed, understarted
spectra are obtained. Longitudinal interference effects occur for appropriate
sweep rates in strongly coupled spin systems and also where the initial
state of the spin system does not correspond to thermodynamic equilibrium
if large flip angles are employed.

Keyword Descriptors: Correlation, interference

Conformation Determination in Small Proteins

Conformational studies using NMR are being carried out on derivatives of Angiotensin II and Bradykinin. Angiotensin II is a naturally occurring linear octapeptide whose biological activities include reversible blood pressure elevation and smooth muscle contraction. Bradykinin is a linear monopeptide which shows various types of biological activity. The important questions concern the relationship of three dimensional structure of these proteins with their biological activity. Various derivatives of these naturally occuring analogs have been synthesized and their respective activities determined. Carbon-13 NMR studies have been carried out on these derivatives and the spin-lattice relaxation times of the various carbon atoms are being measured. Proton NMR studies have also been done. Studies on 4- -methylphenylalanin Angiotensin II show that the conformation of this derivative is quite different from that of the naturally occuring analog Angiotensin II. Nevertheless, both molecules show similar biological activity.

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Theory and Measurement of Intermolecular Forces

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: V. A. Parsegian,   PSL,DCRT
         G. H. Weiss   PSL,DCRT
         J. E. Kiefer   PSL,DCRT
Others: M. Shrader   Naval Weapons Research Laboratory
         R. P. Rand   Brock University
         D. M. LeNeveu   Brock University
         D. Gingell   Middlesex Medical School

COOPERATING UNITS (if any)

LAB/BRANCH

Physical Scineces Laboratory

SECTION

INSTITUTE AND LOCATION
Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.2	OTHER: 0.3

SUMMARY OF WORK (200 words or less - underline keywords)

This project aims to understand the role of long range forces on biological phenomena. A major topic has been the measurement of forces between phospholipid bilayer membranes immersed in water. An accurate procedure for calculating many body forces between spheres of equal radius has been developed.

PHS-6D40

Theory and Measurement of Intermolecular Forces

We have made good progress in developing methods for computing and
detecting intermolecular forces.   This has been accomplished in model
cell membranes immersed in water and in the study of surfaces on which
thin films of water will spread.   .

In the area of force computation, we have developed efficient and
accurate methods for deriving forces between spherical particles.
Similarly we have determined the influence on the force of polymers
coating these particles.   Both formulations are useful in understanding
colloidal aggregation where van der Waals attraction forces are expected
to cause colloidal particles to come together but fudge-free estimates
of force magnitude are difficult. We are developing expressions for the
cohesive energy of atoms in solids and liquids. We expect to be able to
understand the observed work of vaporization of liquids (a phenomenon
for which there is as yet no understanding based on the theory of inter- ·
molecular forces) and possibly to estimate the head required to effect solid-
to-liquid transitions observed in cell membranes.

During a summer project we were able to take high-frequency
spectroscopic data from the Oak Ridge National Laboratory and the
University of Tennessee and reduce this to a form suitable for computation.
This is currently the most promising avenue for determining long-range
van der Waals forces between large bodies.

With Professor Peter Rand of Brock University we have successfully
made measurements of forces between phospholipid bilayer membranes.
This includes the first known estimate of the van der Waals force between
bodies in water.   The results published so far are the beginning of a
series of systematic studies on the physical properties of cell membrane
lipids. We hope to extend these then to direct observations of forces
between natural cell membranes.

With Dr. David Gingell of London, England we have been studying the
interactions of red cells with each other and with artificial materials.
Guided by the theory of forces developed in this laboratory we have
devised experiments demonstrating that cells can be held to artificial
surfaces by long-range electromagnetic forces.

With Dr. Malcom Schrader of the Naval Weapons Research Laboratory we
continue to work on the formation of films on clean gold surfaces. We have
been able to show why minute amounts of contaminant will spoil the wetting
of gold and why earlier theories wrongly described the spread of water
on non-aqueous surfaces.

Publications:

Parsegian, V. A.: Long range van der Waals forces. in <u>Physical Chemistry</u>: Enriching Topics from Colloid and Surface Science, ed. by .I. van Olphen and K. J. Mysels, THEOREX, La Jolla, Calif. 1975.

Parsegian, V. A.: A comment on models of ion transport across cell membranes. <u>Transactions of the ASME</u>, 276-278, (1975).

Shih, A. and Parsegian, V. A.: Van der Waals forces between heavy alkali atoms and gold surfaces: Comparison of measured and predicted values. <u>Physical Review 12A</u>, 835-841 (1975).

Parsegian, V. A.: Ion-membrane interactions as structural forces. in <u>Carriers</u> and <u>Channels</u> <u>in</u> <u>Biological</u> <u>Systems</u>, ed. by A.Shamoo, Annals of the National Academy of Science, <u>264</u>, 161-174, (1975).

LeNeveu, D. M., Rand, R. P., Gingell, D. and Parsegian, V. A.: Apparent modification of forces between lecithin bilayers. <u>Science</u>, <u>191</u>, 399-400,(1976).

LeNeveu, D. M., Rand, R. P. and Parsegian, V. A.: Measurement of forces between lecithin bilayers. <u>Nature</u>, <u>259</u>, 601-603, (1976).

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

The Role of Electrostatic Forces in the Organization and Properties of Macromolecular Systems

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Stephen L. Brenner, Staff Fellow,   PSL,DCRT
Other: V. A. Parsegian, Physicist   PSL,DCRT
        R. E. Gelman, Laboratory of Biochemistry   NIDR

COOPERATING UNITS (if any)

Laboratory of Biochemistry, NIDR
David Gingell, Middlesex Hospital, London, England

LAB/BRANCH
            Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Div. of Computer Research & Technology, NIH, BEthesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.8	0.2

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the project is to probe the role of electrical forces in macromolecular solutions and in organized macromolecular arrays. Studies of the order-disorder phase transitions in suspensions of rod-like viruses and spherical polyelectrolytes have been completed and further analysis of melting transitions is in progress. The swelling pressure of the cornea has been investigated and an explanation for previously anomalous experimental results has been proposed. Studies of the electrostatic interactions between membranes including image forces are being completed and quantitative modifications of previously computed forces have been obtained. Preliminary studies are in progress to examine the role of electrical forces in protein-polysaccharide interactions.

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PHS-6040

Order-Disorder Phenomena in Macromolecular Systems

These studies are designed to probe the role of electrostatic forces in determining the mutual arrangement of macromolecules in aqueous salt solutions. We have completed a theoretical study of the role of long-range forces in determining the phase behavior of solutions of the rod-like tobacco mosaic virus in aqueous salt solutions. The predominant mechanism for forming the observed ordered gels of these viruses has been found to be an excluded volume effect; balancing long-range attractive (electrodynamic) and repulsive (electrostatic) forces are not of primary importance. The knowledge gained in study may provide insight into order in phenomena in a variety of systems, e.g. microtubular arrays, collagen arrays in the cornea, and gels of sickle-cell hemoglobin.

In an effort to better understand melting transitions in general we have developed a model for the observed order-disorder transition in suspensions of charged polystyrene spheres. The model explains the phase transition in terms of an excluded volume effect modified to allow for the strong repulsive interactions due to the charges on the spheres. The resulting phase diagram is in excellent qualitative agreement with experiment. Further work is planned to calculate melting properties of these systems and perhaps to experimentally study the structure of the ordered arrays of polystyrene by quasielastic laser light scattering. Such studies should extend our understanding of phase transitions in general, and of the melting transition in particular.

Selected Studies on the Influence of Electrical Forces on the Observed Properties of Macromolecular Arrays

We have derived a suggested explanation for the "anomalous" swelling pressure of the cornea. The tendency of the cornea to swell decreases with increasing temperature where all previous theories predict the reverse. A major force for the swelling (which leads to opacity) is found to be electrostatic in origin and an analysis of the electrostatic interaction indicates that its behavior with temperature is in agreement with that observed experimentally. Experimental test of the hypothesis have been proposed.

We are currently completing a study on the theory of membrane interactions which includes so-called "image-forces", i.e. the forces mobile salt ions feel when in the vincinity of a boundary between dielectrically distinct materials. The neglect of these forces can in some cases lead to significantly different results for the computed force of membrane interaction. Applications to the study of cell-cell and cell-substrate interactions are envisioned.

Preliminary studies are planned to examine the role of charge-charge interactions in observed properties of polysaccharide-protein solutions in collaboration with R. E. Gelman of the NIDR. These systems are models for the more complex collagen-mucopolysaccharide matrix found in connective tissue. The precise location and function of the poly-saccharides and their observed strong influence on the helical state of cationic poly-amino acids will be investigated.

Publications:

Brenner, S. L. and Parsegian, V. A.: The role of long-range forces in ordered arrays of tobacco Mosaic virus. Nature 259, 632-635, 1976.

Brenner, S. L. and Parsegian, V.A.: Suggested explanation for the anomalous temperature dependence of the corneal swelling pressure. Exp. Eye Res., 22, 95-99, 1976.

Brenner, S. L.: A semiempirical model for the phase transition in polystyrene latexes. J. Phys. Chem. (to appear, 6/76).

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities   1. DCRT

2. LABORATORY OF APPLIED STUDIES   3. Eugene K. Harris
                                                    Chief

The following statement, revised from previous years as the work of the
laboratory has matured, describes the purposes of this laboratory: 1)
In collaboration with biomedical scientists, applies mathematical theory
and computing science to the development, testing and improvement of
mathematical models of physiological processes, with particular attention
to dynamic flow processes, diffusion of substrate to tissues and macro-
molecular interactions; 2) In collaboration with clinicians, develops and
applies statistical theory and computer programming systems to create new
or improved techniques for the diagnosis and evaluation of disease and
assessment of the effects of treatment; 3) Engages in independent research
in applied mathematics, statistics, and computer systems necessary to
provide a sound theoretical basis for methods used in collaborative
studies, with particular emphasis on applied mathematics, differential
equations, numerical analysis, computer graphics, components of variance
analysis, time series analysis.

To facilitate these functions, LAS consists of two sections in addition
to the chief's office: 1) Applied Mathematics Section, headed by
John E. Fletcher, Ph.D., an applied mathematician, and currently including
specialists in applied mathematics, numerical analysis, computer science
and mathematical physiology; 2) Medical Applications Section, headed by
James J. Bailey, M.D., including physicians, electronic (biomedical)
engineers and computer systems analysts. The chief, LAS, is a
biostatistician.

Rather than attempt to summarize here the past year's experience in each
of the laboratory's projects, several new initiatives begun this year
will be described:

    1. (a) Clinical documentation of computerized ECG interpretation, and
(b) computer-based system for functional mapping of parameters from reno-
graphic studies in nuclear medicine.

        Both these projects were initiated by LAS and involve the assessment
of noninvasive, computer-supported techniques for diagnosis of heart and
renal disease respectively. Computerized ECG interpretation via telephone
lines is practiced now throughout the United States and in many other
countries. Previous evaluations by LAS of several computer systems in
this area were based on comparisons with independent diagnoses by a panel
of NIH cardiologists. The current project will strengthen the basis for
evaluation in those cardiovascular diseases leading to left ventricular
hypertrophy such as valvular disease or hypertension. Cardiac catherization

data and/or echocardiograms have been collected so far in 300 NIH patients from whom ECG records were also obtained. Two ECG programs, the IBM (Bonner) and the AVA (Pipberger) programs, already shown by earlier comparisons to be superior to several other interpretive programs, will be reevaluated on the basis of this new clinical documentation. It is expected that an additional 100 patients will be included in the study during the next fiscal year.

Functional mapping is a technique whereby parameters associated with the uptake and washout of radionuclides in a given organ system (e.g., rates of change, maximal levels) are displayed graphically over time within defined regions of interest in the organ. The large volume of information required demands the use of dedicated computer systems established in the Nuclear Medicine Department of the Clinical Center through a collaborative project of many years' standing with LAS. Applied to studies of kidney disease, functional mapping has been able to improve diagnostic accuracy in many cases: for example, to distinguish an intrarenal obstruction in the cortiocomedullary area while confirming the absence of extrarenal blockage. This distinction could not have been made from the routine renograms.

2. Computer simulation of physiologic systems

There is a growing literature on the application of computers to the simulation of various physiologic systems. Early efforts in this area involved either imitating physiologic behavior under some assumed optimal thermodynamic state, or else fitting a simple mathematical expression of an entirely empirical nature. More recently, the simulations have become more elaborate, particularly with respect to respiratory, endocrinologic and cardiovascular-renal systems, but less amenable to use by practicing physicians because most of the parameters involved cannot be measured in human patients. However, with the rapid development of knowledge about the operating details of real systems in normal and diseased states, there is a growing opportunity for useful application of computer simulations based on known physiologic pathways and including more comprehensive information than the physician can retain in his own mind. Simulation programs should be particularly useful for advising on the multiple effects of proposed therapy. As part of its effort in this area, LAS has entered into a small contract with the Department of Physiology at George Washington University Medical School who have for many years used cardiovascular and acid-base simulation programs in teaching physiology to medical students. Under this contract, several existing simulations in the cardiovascular-renal area will be evaluated against a framework of pathways known to be essential in homeostatic control. Guided by this contract effort, to be completed in early 1977, LAS intends to reexamine cardiovascular-renal simulation, emphasizing renal functions in acid-base balance and mineral metabolism. We hope that such a program will integrate these pathways in a more satisfactory manner than existing programs. Further, we hope to arrange to have the new program tested on a pilot basis by interested physicians in an urology clinic. This in itself will not be new, for example, one highly regarded acid-base balance program has already received a fair amount of such practical experience. However, the clinical utilization of physiologic simulation programs are still

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uncommon despite the growing use of other computer aids in medical practice (e.g., automated ECG interpretation, burn control programs, etc.).

3. Application of time series models to periodic biochemical screening of individuals

One of the continuing research projects of this Laboratory has involved the estimation and interpretation of intra- and interindividual variance components in common biochemical tests, based on repeated blood samples from healthy individuals. The size of these biological variations relative to analytic error has also been investigated. Analysis of weekly series of samples from small groups of normal volunteers here and abroad has shown that in most chemical and hematological tests, the variation observed within the average individual is less, often much less, than that observed in data drawn from a large number of persons. From this it follows that the conventional, population-based "normal range" is often not sensitive enough to detect statistically significant (and perhaps clinically significant) deviations from an individual's past record. Development of individualized reference values requires construction and testing of statistical time series models accounting for intrapersonal variations within the healthy state as well as analytic errors of measurement. Application of such a model leads to the estimation of a critical value which if exceeded by a new observation would indicate a nonrandom change in the individual's state. Several such models have been designed and adapted to short series of periodic observations. They are currently being applied on a pilot basis to a small group of presumably healthy persons enrolled voluntarily in a periodic health screening program. Planning is now underway between LAS and at least one collaborating group to apply these forecasting methods on a much larger scale in such screening programs. If they prove of value in large-scale use, they may represent a significant contribution to the early detection of chronic disease.

4. Collaborative studies: LAS and Pulmonary Branch, NHLI

Since FY 73, this Laboratory has collaborated with the Department of Nuclear Medicine and the NHLI in the application of computer-based applications of nuclear medicine techniques to the assessment of ventilation (airflow) and perfusion (blood-flow) in the lungs. Recently, this association has begun to develop into closer cooperation with the newly-formed Pulmonary Branch (NHLI). The ultimate goal is the formulation of mathematical models and computer programs to simulate the dynamics of pulmonary gas exchange and the mechanics of breathing. A number of simulation programs for gas exchange exist in the literature and will be studied to select one or parts of several for possible implementation and further development. In both areas the aim will be to assist in understanding the effects of anatomical changes, due to disease or age, on these pulmonary functions. Mathematical models, implemented as computer programs, contribute to this goal by providing immediate information on the effects of deliberate, controlled disturbances to the system.

As in past years, staff members of this Laboratory contributed this year to teaching programs at NIH. Courses taught included seminars on time series analysis of clinical data (Harris) and the use of mathematical models in analyzing data on protein binding of drugs and other ligands (Fletcher). Many LAS staff are also faculty members in the Stride and FAES evening educational programs. Courses in mathematics and computer science are offered to interested personnel after normal working hours.

The following is a list of LAS publications and papers accepted for publication during FY 76:

1. Agress, H., Jr., Levenson, S.M., Gelfand, M.J., Green, M.V., Bailey, J.J., Johnston, G.S.: Application of computer-generated functional maps in radionuclide renography. Proceedings of the Fifth Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. CONF-750124, U.S. Atomic Energy Commission Technical Information Center, Oak Ridge, Tennessee, 1975, 180-194.*

2. Agress, H., Jr., Levenson, S.M., Gelfand, M.J., Johnston, G.S., Bailey, J.J.: Utility of computer-generated images in 130 radionuclide renography studies. Transactions of the American Nuclear Society, 22: 125, 1975.

3. Bailey, J.J., Horton, M.R., Itscoitz, S.B.: The importance of reproducibility testing of computer programs for electrocardiographic interpretation: Application to the automatic vector-cardiographic analysis program (AVA3.4). Computers and Biomedical Research (in press).

4. Eisenberg, J.B., Eisenberg, M.F., Shafter, M.J.: An alternate cycle reversing electronic switch for evoked responsing computing. Proceedings of the 28th ACEMB, 17: 7, September 1975.

5. Fletcher, J.E.: A model describing the unsteady transport of substrate to tissue from the microcirculation. SIAM J. Applied Math., 29: No. 3, September 1975.

6. Fletcher, J.E.: Distributed parameter modeling of the microcirculation. Systems Analysis of Biomedical Transport, edited by D. D. Reneau, Marcel Dekker, Inc., New York, 1976 (in press).

7. Fletcher, J.E.: Some model results on hemoglobin kinetics and its relationship to oxygen transport in blood. Oxygen Transport to Tissue, edited by G. Thews and J. Grote, Plenum Press, New York, 1976 (in press).

8. Green, M.V., Agress, H., Jr., Brody, W.R., Pearlman, A.S., Douglas, M.A., Ostrow, H.G., Redwood, D.R., Itscoitz, S.B., Bailey, J.J., Johnston, C.S.: A comparison of high temporal resolution left ventricular volume curves before and after mitral replacement. Proceedings of the Fifth Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. CONF-750124, U.S. Atomic Energy Commission Technical Information Center, Oak Ridge, Tennessee, 1975, 37-47.*

9. Green, M.V., Bacharach, S.L., Douglas, M.A., Line, B.R., Ostrow, H.G., Redwood, D.R., Bailey, J.J., Johnston, G.S.: The measurement of left ventricular function and the detection of wall motion abnormalities with high temporal resolution ECG-gated scintigraphic angiocardiography. IEEE Transactions in Nuclear Science, 1976 (in press).

10. Green, M.V., Bailey, J.J., Ostrow, H.G., Douglas, M.A., Pearlman, A.S. Brody, W.R., Itscoitz, S.B., Redwood, D.R., Johnston, G.S.: Computerized EKG-gated radionuclide angiocardiography: a non-invasive method for determining left ventricular volumes and local myocardial dyskinesia. Computers in Cardiology. IEEE Computer Society, Long Beach, Ca., 1975 (in press).

11. Harris, E.K.: Some theory of reference values. I. Stratified (categorized) normal ranges and a method for following an individual's clinical laboratory values. Clin. Chem. 21: 1457-1464, 1975.

12. Harris, E.K.: Some theory of reference values. II. Comparison of some statistical models of intraindividual variation in blood constituents. Clin. Chem. , 1976 (in press).

13. Line, B.R., Jones, A.E., Crystal R.G., Johnston, G.S., Bailey, J.J.: An algorithm for the selection of lung margins in scintigraphic ventilation-perfusion studies. Proceedings of the Sixth Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine, 1976 (in press).

14. Ostrow, H.G., Green, M.V., Scott, R.N., Douglas, M.A., Bailey, J.J., Johnston, G.S.: Simultaneous measurement of the variation of left ventricular volume by non-invasive ECG gated scintigraphic angiocardiography and by electromagnetic flowmeter. Proceedings of 28th ACEMB, September 1975, 127.

15. Pottala, E.W., Mortimer, J.A.: A hybrid compartmental model for the alligator purkinje cell. 1: Preferred somatopetal conduction of dendritic spikes and soma-axon interaction. J. Neurosci. Res. 1: 207-225, 1975.*

16. Wright, G., Wasserman, D., Pottala, E.W., Dakes-Dubos, F.: The effect of general fatigue on isometric strength-endurance measurements and the electromyogram of the biceps brachili. <u>J. American Industrial Hygiene Assoc.</u> (in press).

* Reported in FY 75 as "in press".

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER
		Z01 CT 00002-06 LAS

PERIOD COVERED   July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Evaluation of Computer Systems for ECG Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. J. Bailey	Head, Medical Applications Section	LAS DCRT
OTHER:	M. R. Horton	Computer Systems Analyst	LAS DCRT
	S. B. Itscoitz	Chief, ECG Laboratory	CB NHLI
	D. D. Savage	Clinical Associate	CB NHLI

COOPERATING UNITS (if any)
Cardiology Branch, NHLI, NIH

LAB/BRANCH   Laboratory of Applied Studies

SECTION   Medical Applications Section

INSTITUTE AND LOCATION   DCRT, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS: 1.3	PROFESSIONAL: 1.2	OTHER: 0.1

SUMMARY OF WORK (200 words or less — underline keywords)

To assess the usefulness of computer systems for ECG analysis based upon clinical findings from cardiac catheter laboratory studies and echocardiography.

PHS-NIH
Individual Project Report
July 1, 1975 through June 30, 1976

Project Title: Evaluation of Computer Systems for ECG Analysis

Previous Serial Number: Same

Principal Investigator: J. J. Bailey

Other Investigators: M. R. Horton, S. B. Itscoitz, D. Savage

Cooperating Units: Cardiology Branch, NHLI; ECG Laboratory, CC

Man Years:

    Total: 1.3
    Professional: 1.2
    Others: 0.1

Project Description:

    Objective:

        To assess the usefulness of computer systems for ECG
        analysis.

    Progress during FY 76:

        This work begun in FY 70 has involved the study of various
        methods for ECG analysis, including the use of orthogonal
        transforms (Fourier, Hambly), use of vector loops, and use of
        computer programs to interpret resting ECGs. In FY 74 a
        clinical evaluation of three such programs was published.
        In FY 75 the IBM program was implemented for routine daily
        use on the NIH campus. In FY 76 a 360 version of AVA3.4
        (Pipberger) program was certified and has been clinically
        tested. (publication 1).

        Also in FY 76 ECG data on 400 NIH patients has been collected.
        Clinical documentation of each patient's status in the form
        of cardiac catheter studies and/or echocardiogram has been
        collected in 300 of these cases. These data will be used to
        test the sensitivity and specificity of computer algorithms
        for determining hypertrophy and/or chamber overload in the
        ECG using the IBM and AVA programs.

The Royal Glasgow Infirmary has sent ECG data from several
hundred documented cases and a procedure for comparing
the IBM program with the RGI program is being designed.

In FY 76 a certified 360 implementation of version E of the
Public Health Service was achieved. MAS is cooperating
with Cardiology Department of the Naval Regional Medical
Center in San Diego, California in testing the usefulness
of this program.

Proposed Course:

The testing of these programs with clinically documented data,
i.e., cases with correlative data from cardiac catheter
laboratory studies, echocardiography, or scintigraphic
studies, is expected to to be completed within FY 78.

Keywords:

ECG analysis, heart disease, computer programs, clinical
applications, clinical evaluations.

Publications:

1. Bailey, J.J., Horton, M.R., and Itscoitz, S.B.: The
    importance of reproducibility testing of computer
    programs for electrocardiographic interpretation:
    Application to the automatic vectorcardiographic
    analysis program (AVA3.4). Computers and Biomedical
    Research (in press).

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Computer Systems for Nuclear Medicine

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. J. Bailey	Head, Medical Applications Section	LAS DCRT
	M. V. Green	Chief, Applied Physics Section	NM CC
	B. R. Line	Senior Assistant Surgeon	LAS DCRT
OTHER:	G. S. Johnston	Chief, Nuclear Medicine Dept.	NM CC
	R. G. Crystal	Chief, Pulmonary Branch	PB NHLI
	D. R. Redwood	Chief, Cardiovasc. Diagnostic Section	CB NHLI
	M. A. Douglas	Computer Systems Analyst	LAS DCRT
	H. G. Ostrow	Engineer	CSL DCRT
	S. L. Bacharach	Physicist	NM CC
	S. M. Levenson	Staff Fellow	NM CC
	R. Dunham	Computer Specialist	NM CC

COOPERATING UNITS (if any)
Nuclear Medicine Dept., Clinical Center, NIH
Cardiology Branch, NHLI, NIH
Pulmonary Branch, NHLI, NIH
Computer Systems Laboratory, DCRT, NIH

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS: 2.7	PROFESSIONAL: 2.6	OTHER: 0.1

SUMMARY OF WORK (200 words or less - underline keywords)

To provide computer-based mathematical analysis in support of diagnostic activites in the Nuclear Medicine Department and in collaborating Institutes. Applications include: computerized ECG-gated radionuclide angiocardiography studies of left ventricular performance and dyskinesia; scintigraphic studies of regional myocardial blood flow; pulmonary ventilation-perfusion scintigraphy; functional maps of radionuclide renography; and image processing of scintigraphic data.

PHS-6040
(12-75)

PHS-NIH
Individual Project Report
July 1, 1975 through June 30, 1976

Project Title: Computer Systems for Nuclear Medicine

Previous Serial Number: Same

Principle Investigators: J. J. Bailey, B. R. Line (LAS)
                           M. V. Green (NM/CC)

Other Investigators: M. A. Douglas, R. Dunham, H. G. Ostrow,
                       S. L. Bacharach, S. M. Levenson, G. S. Johnston,
                       D. R. Redwood, S. B. Itscoitz, R. G. Crystal,
                       J. D. Fullmer

Cooperating Units: Nuclear Medicine Department, Clinical Center, NIH
                     Cardiology Branch, NHLI
                     Pulmonary Branch, NHLI
                     Surgical Neurology Branch, NINDS
                     Computer Systems Laboratory, DCRT

Man Years:

    Total: 2.7
    Professional: 2.6
    Others: 0.1

Project Description:

    Objectives:

        To provide computer-based analytic methods in support of
        diagnostic activities in the Nuclear Medicine Department
        of the Clinical Center and in collaborating Institutes.

    Progress during FY 76:

        Since FY 72 LAS with support from the Computer Systems Laboratory,
        DCRT, and in collaboration with the Nuclear Medicine Department,
        Clinical Center, has accomplished the specification, selection,
        and acquisition of a minicomputer system which was mated to
        two gamma scintillation cameras in NM. Subsequently LAS
        programmers have developed and implemented extensive
        software (on both the NM minicomputer system and the PDP-10
        facility in DCRT) which has found wide-ranging applications,
        including fitting of mathematical models, mapping the

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parameters of such models over time and in different regions of an organ; for image restoration by deconvolution and for non-restorative image enhancement; and interpolation, expansion, and contraction of image arrays.

In FY 76 the development of the extended nuclear utility (ENU) system was nearly completed and documentation begun. ENU allows the rapid modular construction of complex processing programs using newly developed modules as well as modules from a library of already developed algorithms. ENU has already proved useful in the construction of a batch mode processing program which analyzes scintigraphic ventilation-perfusion data (Publication 1).

The most important clinical application completed this year (begun in FY 74) has been the computer-based ECG-gated technique of radionuclide angiocardiography. Because of its non-invasive, non-surgical nature, requiring no anesthesia and less radiation dose than a single chest Xray, this study can be repeated frequently or can be performed on patients too sick to undergo cardiac catheterization. During FY 76, 100 patients from the Cardiology Branch, NHLI were studied (Publications 2-5). In most of these patients, the timing relationships (ejection phase, fast filling phase, slow filling phase, etc.), the indices of myocardial contractility (ejection fraction, peak fractional ejection rate, etc.), and detection of wall motion abnormalities compared well with similar observations in contrast angiography.

Another important computer-based technique, begun in FY 75, is ECG-gated myocardial scintigraphy during rest and stress using radionuclide labeled macroaggregated human serum albumin or albumin microspheres. This technique promises to help determine the pathophysiologic effect of anatomic lesions revealed by coronary angiography and thereby add considerably to the evaluation of patients who might be candidates for coronary artery surgery. In FY 76 double isotope studies have been performed on 27 patients. The double isotope technique is so called because albumin particles can be tagged with radioisotopes of iodine or technetium. At the time of routine coronary angiography, one isotope is injected into the coronary ostia at a resting heart rate and other is injected at a increased heart rate which is induced by pacemaker. Radioactive Thallium is being studied as a possible replacement for labeled macroaggregated albumin; the advantage of Thallium is that it can be given intravenously and would allow the study of coronary flow to be noninvasive.

A third computer-based method involving functional maps (see above) in radionuclide renography was begun in FY 73.

In FY 74 thru FY 76 this method was applied to 130 patients and was found to enhance the detection of functional abnormalities in more than one-third of the cases (publications 6 and 7). In one case the functional maps showed slight residual impairment of function in the left kidney 18 months after removal of a renal stone and relief of obstruction. The routine scintigraphic studies (without computer processing) were interpreted as normal. In another case, the functional maps showed a normal uptake of isotope over the corticomedullary areas but a delay over the pelvic region of the left kidney. The functional maps also showed a delayed washout of isotope from a wedge-like corticomedullary area in the mid and lower pole of the kidney but washout from the pelvis was normal. These results meant that there was an intrarenal obstruction in this wedge-like area and that there was no extrarenal obstruction (e.g. a blocked ureter). This interpretation could not be made from the routine scintigraphic study which was read as compatible with extrarenal obstruction.

Use of a computer-based method for scanning the status of ventilation and perfusion in the lungs began in FY 73. At that time it proved useful in following the changes in pulmonary dynamics in patients who underwent surgical repair of valvular heart disease. In FY 74 through FY 76 this method was refined by the incorporation of volume gating and by automatic edge detection (publication 1). This method of measuring ventilation/perfusion ratios combined with data from the Pulmonary Branch (NHLI) will form the basis of mathematical models to simulate the dynamics of pulmonary gas exchange and the mechanics of breathing. Such models may have significance in determining more precisely the pulmonary status of a patient and his prognosis. These studies will continue in cooperation with the Applied Mathematics Section, LAS.

In FY 75 computer based methods for determining regional cerebral blood flow were designed and in FY 76 these methods were used to study monkeys in whom cerebral infarction was experimentally induced. A paper is in preparation, describing these studies. It was found that the infarct must be at least one centimeter in diameter in the monkey in order to produce reliable results by this technique.

In FY 76 a package of image processing routines (IMAGE) was developed on the PDP 10 system. This package is capable of several functions: e. g. edge detection, spatial derivatives, iterative deconvolution, noise detection, and application of selective filters. Currently it is being used to test the effectiveness of various image enhancement methods on scintillation data using a point response function and

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realistic scintillation phantoms - for example, a camera
response image to a technetium point source and an irregular,
somewhat ellipsoidal, egg-shell phantom filled with technetium
in solution.

Keywords:

Publications:

1. Line B.R., Jones A.E., Crystal R.G., Johnston G.S.,
    and Bailey J.J.: An algorithm for the selection of
    lung margins in scintigraphic ventilation-perfusion
    studies. Proceedings of the Sixth Symposium on Sharing
    of Computer Programs and Technology in Nuclear Medicine,
    1976 (in press).

2. Green M.V., Bacharach S.L., Douglas M.A., Line B.R.,
    Ostrow H.G., Redwood D.R., Bailey J.J., and Johnston G.S.:
    The measurement of left ventricular function and the
    detection of wall motion abnormalities with high
    temporal resolution ECG-gated scinitigraphic
    angiocardiography. IEEE Transactions in Nuclear Science,
    1976 (in press).

3. Green M.V., Agress H.Jr., Brody W.R., Pearlman A.S.,
    Douglas M.A., Ostrow H.G., Redwood D.R., Itscoitz S.B.,
    Bailey J.J., and Johnston G.S.: A comparison of high
    temporal resolution left ventricular volume curves before
    and after mitral valve replacement. Proceedings of the
    Fifth Symposium on Sharing Computer Programs and
    Technology in Nuclear Medicine. CONF-750124, U.S. Atomic
    Energy Commission Technical Information Center, Oak Ridge,
    Tennessee, 1975, 37-47. *

4. Ostrow H.G., Green M.V., Scott R.N., Douglas M.A.,
    Bailey J.J., and Johnston G.S.: Simultaneous measurement
    of the variation of left ventricular volume by non-invasive
    ECG gated scintigraphic angiocardiography and by
    electromagnetic flowmeter. Proceedings of 28th ACEMB,
    Sept. 1975, 127.

5. Green M.V., Bailey J.J., Ostrow H.G., Douglas M.A., Pearlman A.S., Brody W.R., Itscoitz S.B., Redwood D.R., and Johnston G.S.: Computerized EKG-gated radionuclide angiocardiography: a non-invasive method for determining left ventricular volumes and local myocardial dyskinesia. Computers in Cardiology. IEEE Computer Society, Long Beach, Ca., 1975 (in press).

6. Agress H.Jr., Levenson S.M., Gelfand M.J., Green M.V., Bailey J.J., and Johnston G.S.: Application of computer-generated functional (parametric) maps in radionuclide renography. Proceedings of the Fifth Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. CONF-750124, U.S. Atomic Energy Commission Technical Information Center, Oak Ridge, Tennessee, 1975, 180-194 *

7. Agress H.Jr., Levenson S.M., Gelfand M.J., Johnston G.S., and Bailey J.J.: Utility of computer-generated images in 130 radionuclide renography studies. Transactions of the American Nuclear Society, 22: 125, 1975.

* Reported "In Press" in FY 75.

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PER. OD COVERED

July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Investigations of Physiologic Signals and Simulation Models by Hybrid Computing

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: E. W. Pottala   Elec. Engineer   LAS DCRT

OTHER: J. J. Bailey   Head, Medical Applications   LAS DCRT
                              Section
         J. B. Eisenberg   Elec. Engineer   LAS DCRT
         M. R. Horton   Computer Systems Analyst   LAS DCRT

COOPERATING UNITS (if any)

Neurosurgery Dept., University of Minnesota
National Institute of Occupational Safety and Health, NIH
Dept. of Biomedical Engineering, George Washington University

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Medical Applications Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS: 1.9	PROFESSIONAL: 1.8	OTHER: 0.1

SUMMARY OF WORK (200 words or less - underline keywords)

1. To develop physiologic simulation models using hybrid computing techniques.

2. To develop the LAS mini-computer system as a research tool for handling physiologic signals such as electrocardiogram, electromyogram, electroencephalogram, ultra sonogram, and analog blood pressure recordings.

PHS-6040
(12-75)

PHS-NIH
Individual Project Report
July 1, 1975 through June 30, 1976

Project Title: Investigations of Physiologic Signals and Simulation
                 Models by Hybrid Computing

Previous Serial Number: Same

Principal Investigators: Erik Pottala

Other Investigators: J. J. Bailey, J. B. Eisenberg, J. Mortimer,
                       M. Horton

Cooperating Units: National Institute of Occupational Safety and
                     Health; University of Minnesota, Minneapolis,
                     Minnesota, Department of Biomedical Engineering,
                     George Washington University

Man Years:

       Total: 1.9
       Professional: 1.8
       Others: 0.1

Project Description:

       Objectives:

              1.   To develop physiologic simulation models using
                   hybrid computing implemented on the LAS laboratory
                   mini-computer, e.g., in neurophysiology to simulate
                   neural networks and central nervous subsystems
                   (e.g., cerebellum).

              2.   To develop the LAS mini-computer system as a research
                   tool for handling physiologic signals: e.g.,
                   electrocardiogram, electroencephalogram, electromyogram,
                   and ultra sound records.

       Progress during FY 76:

       Neural network simulation employing physiologically realistic
       hardware neural models, which incorporate a distributed input

system (analogous to a dendritic net) with simulated action potentials, has been pursued since FY 72. In FY 74 a neural hardware model interfaced with the mini-computer system was used to study a small neural net and show how an action potential can modify the shape and duration of post-synaptic potentials and their spatio-temporal interactions. In FY 75 this work with small neural nets and their reciprocal inhibition-excitation behavior was extended to the study of the cerebellum (publication 1).

Development of the LAS mini-computer system has continued during the past year. The system has been interfaced with the Marquette tape drive (for routine ECGs from the Clinical Center); with the Honeywell 7600 analog tape transport; with a general purpose switch- filter network; with a real time spectral analyzer and ensemble averager; and with a neural control panel for the model work described above.

This system is capable of processing various analog (physiologic) signals. For example, in FY 74 through 76, electromyographic signals collected at the National Institute of Occupational Safety and Health from stressed subjects were analyzed by this system using the spectrum analyzer. The optimum ranges of power spectra for this study were determined by this analysis and the results were used to study muscle fatigue (Publication 2).

Another example involves ECG data collected at the Royal Glasgow Infirmary (see 3.2). These data contain varying levels of 50 Hz. noise. With the aid of the LAS mini-computer system, the character of this noise was studied and an analog notch filter was designed to suppress it. The effect of this filter on the data and ultimately upon the diagnostic statements of an ECG analysis program were easily studied by the aid of the mini-computer system. The optimal parameters (attenuation and window size) of the filter could then be selected, in terms of a trade-off between noise suppression and artifact generation.

A general advantage of this system which has been demonstrated before in other studies (ECG and pressure from monkey preparations) is that an investigator can automatically pre-process (edit, filter, and digitize) dynamic physiologic data so that optimal use of a large scale digital computer can be obtained. It is anticipated that this system will be very efficient in processing electroencephalographic data from evoked potential studies on patients at George Washington University Medical Center, which will require special techniques in noise recognition and filtering (Publication 3).

A new project in FY 76 involves computer processing of ultrasound data, with special emphasis on echocardiography,

which will be used to study intracardiac dynamics. The first
difficulty is that the ultrasound transducers produce analog
data with frequencies in the megaHertz range, a rate which is
10-20 times the capacity of the usual mini-computer. A
hardware device which digitizes the ultrasound signal at a
megaHertz rate, temporily stores a buffer, and subsequently
transfers the data to a mini-computer at a kiloHertz rate has
been acquired and is currently being interfaced with the
Hewlett Packard mini-computer system which is in the Nuclear
Medicine Department at the Clinical Center. Subsequently this
hardware device will be interfaced to a Picker Ultrasound EDC
which contains the ultrasound transducer and is on order.
The echo data collected by the Nuclear Medicine minicomputer
will be processed by the LAS laboratory minicomputer to
suppress noise and enhance the echo images.

In FY 76 the LAS minicomputer system was upgraded with 16K
additional core, a 1600 BPI magnetic tape drive, and a MAP 100
array processor. A disk pack and grey level CRT are also
planned. These improvements will allow speedy investigation
of image processing algorithms and analysis of ultrasound data
from Nuclear Medicine and NHLI clinical studies.

Keywords:

neurophysiology, hybrid computer, simulation, cerebellum,
signal analysis, electrocardiography, electromyography,
image processing, echocardiography, ultrasound,
electroencephalography.

Publications:

1. Pottala E.W., and Mortimer J.A.: A hybrid
   compartmental model for the alligator purkinje
   cell. 1: Preferred somatopetal conduction of
   dendritic spikes and soma-axon interaction.
   J. Neurosci. Res. 1: 207-225, 1975. *

2. Wright G., Wasserman D., Pottala E.W., and Dakes-Dubos
   F.: The effect of general fatigue on isometric
   strength-endurance measurements and the electromyogram
   of the biceps brachii. J. American Industrial Hygiene
   Assoc. (in press).

3. Eisenberg J. B., Eisenberg M. F., and Shafter M. J.:
   An alternate cycle reversing electronic switch for
   evoked responsing computing. Proceedings of the
   28th ACEMB 17: 7, September 1975.

   * Reported "In Press" in FY75.

PERIOD COVERED

July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Mathematical Modeling of Biological Processes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. E. Fletcher	Head, Applied Mathematics Section	LAS DCRT
OTHER:	B. Bunow	Sr. Staff Fellow	LAS DCRT
	J. Rinzel	Res. Mathematician	MRB NIAMD
	A. Spector	Prof., Univ. of Iowa	
	C. Tidball	Prof., G. Washington Univ.	

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Applied Mathematics Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.8	1.8	

SUMMARY OF WORK (200 words or less - underline keywords)

Complex and interacting biological and biochemical processes are described in terms of mathematical models, (generally complex systems of differential equations) which are studied for their qualitative and quantitative properties. Such results are interpreted to suggest new experiments and to gain insight into the innerworkings of systems too complex to examine by laboratory experiments alone. Present applications are to substrate supply within human and/or animal microcirculatory systems; large scale physiological simulations of cardio-pulmonary functions; to models of drug-protein binding; and to idealized mathematical models of nonlinear cell kinetics.

Project Title: Mathematical Modeling of Biological Processes

Previous Serial Number: Same

Principal Investigators: J. Fletcher, B. Bunow (arrived 9/1/75).

Co-Investigators: A. Spector Univ. of Iowa, Prof. C. Tidball G.W. Univ.
                   J. Rinzel, NIAMDD

Man Years: Professional 1.8

Project Descriptions:

Background and Objectives:

The primary responsibility of the Applied Mathematics
Section is to provide DCRT and the NIH with a broad
spectrum of advanced mathematical competence for
biomathematical modeling and data analysis. This
competence includes both theoretical and applied
techniques, as well as numerical approximation and
computation methods. Each individual in the section
has a primary competence in computer science, mathematics
or physical science, and in addition is intimately
familiar with electronic computing equipment.

Project Tasks, during FY 75:

1. Modeling of Macromolecule-Ligand Binding:

New efforts at consolidation of modeling theories
were undertaken in FY 76 with the objective of
clarifying the meanings and appropriateness of the
various models for the interpretation of drug-protein
interactions. The commonly used models were reexamined,
and a new formulation which includes most previous
models has been developed. A manuscript detailing
these findings is in preparation. A second manuscript
which quantitates the probable in vivo serum fatty acid

distributions and explains competitive displacement of
drugs by these fatty acids has been completed and
was submitted for publication. Continuing efforts in
this area will emphasize techniques for computer
implementation of the new concepts and more testing
with actual laboratory data. A seminar series is being
given to make these concepts and methods directly
available to interested NIH and local area investigators.

2. Mathematical Models and Simulation Programs in Physiology.

The tissue oxygen transport studies reported
in last year's annual report are being merged with
new efforts initiated during FY 76. The effects of
Ph and Bohr shifts of oxyhemoglobin dissociation
in blood have been incorporated into the mathematical
models discussed in the previous annual report. Although
further expansion of these modeling efforts has been
suspended for the present, a new collaborative effort
now underway with the Pulmonary Branch, NHLI, is expected
to provide new areas in which applications of these
modeling studies can be made. Of particular interest
is the modelling of alveolar-capillary gas exchange which
may provide a physical basis for understanding the
mismatching of ventilation and perfusion commonly found
in many lung diseases.

A contract with the George Washington University Department
of Physiology (Professor Charles Tidball) was entered into
during FY 76, to develop a physiological basis for
evaluating and improving existing computer simulations of
cardiovascular-renal function. Detailed analysis of such
programs under this contract has shown that in almost all
cases, they are deficient in the attention paid to the many
interdependent pathways which are affected by pathologic
disturbances to the system. Hence, the programs appear to
achieve proper responses in some variables but not in
others which should also be affected because of the
interdependence of feedback and control pathways. To detect
and correct the nonphysiologic behavior of these computer
simulations, Professor Tidball is developing a general
framework of the essential variables and pathways involved
in maintaining steady state cardiovascular-renal function.
The result will be a series of sets of physiological
relationships devoted to different homeostatic
functions, but interrelated because the same variables are
represented in different sets. Under Professor Tidball's
guidance, this laboratory will then reduce these sets of
relationships to one or more new simulation programs for
potential application to care of patients by practicing
physicians.

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3. Multiple Steady States of Enzyme Kinetics in Cells.

A project concerned with the mathematical modeling of enzyme-catalyzed reactions in cellular compartments was begun in FY 76. The study of preliminary models has revealed the existence of complicated spatial and temporal patterns in the substrate distributions. The nonlinear algebraic and differential equations describing the static and dynamic models of such systems require techniques and concepts that are not well developed in the existing mathematical literature. These methods involve perturbation techniques, bifurcation theory, and continuation procedures. Preliminary investigations reveal that the primary factors in these models appear to be the nonlinear kinetics of the enzyme reaction and the topological arrangement of cellular structures. Two types of kinetics have been studied: 1) single substrate kinetics with substrate inhibition for which a general result is multiple steady states corresponding to a variety of non-uniform patterns of concentration in arrays of identical cells. This behavior may have inferences for embryological differentiation phenomena. 2) substrate-product kinetics with product activation which exhibit limit cycle solutions. Present efforts are directed towards the problem of detecting non-uniform patterns of oscillations in cellular arrays. Goodwin's theory of morphogenesis depends upon the existence of such patterns, but they have not been previously demonstrated even in model systems. Smale has conjectured that at least three components were necessary in order that a system which was non-oscillatory in a single cell, be oscillatory in a cellular array. The present model appears to provide an example in which only two such components show oscillations. Manuscripts detailing these results will be submitted in FY 77.

Keywords:

drug binding, binding models, simulation models, substrate supply models, physiologic simulations, cardiovascular-renal simulations, enzyme kinetics, enzyme-catalyzed reaction models.

PERIOD COVERED

July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

General Mathematical and Computational Collaborative Efforts

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: E. Hill, Jr.   Mathematician   LAS DCRT
OTHER: R. Shrager   Mathematician   LSMM DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Applied Mathematics Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.1	1.1	

SUMMARY OF WORK (200 words or less - underline keywords)

Mathematical modeling and computational procedures in collaboration with research tasks both within DCRT and across the NIH intramural program. Specific applications are least squares and other nonlinear model fitting methods, and a comparative study of data and file-organization for storage and retrieval in large data bases.

Project Title: General Mathematical and Computational
                 Collaborative Efforts

Previous Serial Number: Same

Principal Investigators: E. Hill, J. Ashbrook (transferred to CCB, DCRT,
                           R. Shrager, DCRT   8/11/75)

Man Years: Professional 1.1

Project Description:

1. Nonlinear Model Fitting and Parameter Estimation

    During FY 76 new methods were developed for non-linear curve-fitting
    in the L_1, $(L_1 = \Sigma \mid \bar{y} - \hat{y} \mid_i)$ and L_∞ $(L_\infty = 1 \leq i \overset{max}{\leq} m \mid \bar{y} - \hat{y} \mid_i)$
    norms. These methods use the Simplex Dual algorithm of linear
    programming to fit data, and they provide an alternative to least
    squares (L_2) methods which are unsatisfactory for systems with
    many parameters or a wide range of observational values. The
    Levenberg-Marquardt method for non-linear curve-fitting in the L_2
    norm has been extended to solve the L_∞ norm problem using
    Stiefel's algorithm. The parameters of the fitting approxima-
    tion are determined by Stiefel's algorithm so as to minimize
    the deviations in the L_∞ norm. This iterative method determines
    the model parameters in both linear and non-linear estimation
    problems.

    This method was also used to solve the L_1 and L_∞ norm problem
    using the Simplex Method. The parameters of the fitted model
    are determined by the Simplex Method so as to minimize the
    error in either of the L_1 and L_∞ norms.

    Manuscripts describing this work have been submitted for
    publication.

2. Comparative Study of Large Data Bases

    This new project involves a comparison of methods for
    organizing large amounts of stored data on direct access
    storage devices to facilitate fast retrieval of the

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desired information. Several hybrid methods are being
developed and analyzed along with their data structures.
A comparison criterion will be developed to provide
a measure of performance for each method.

The resulting methodology is expected to have applications to
storage and retrieval schemes for medical records, computer-
aided diagnoses, and other areas requiring search in
very large data or decision files.

3. Computer Graphics and Display Systems:

This project was transferred to CCB DCRT with Mr.
Ashbrook effective 8/11/75.

Keywords:

model fitting, parameter estimation, large data bases,
storage and retrieval, linear programming.

Publications:

1. Fletcher J. E.: A model describing the unsteady transport
of substrate to tissue from the microcirculation.
SIAM J. Applied Math., Vol 29, No. 3, September 1975.

2. Fletcher J. E.: Distributed parameter modeling of the
microcirculation. _Systems Analysis of Biomedical
Transport_, edited by D. D. Reneau, Marcel Dekker, Inc.
New York, 1976 (in press).

3. Fletcher J. E.: Some model results on Hemoglobin
Kinetics and its Relationship to Oxygen Transport in
Blood. _Oxygen Transport to Tissue_, edited by G. Thews
and J. Grote, Plenum Press, New York 1976 (in press).

PERIOD COVERED
July 1, 1975 to June 30, 1976

TITLE OF PROJECT (80 characters or less)

Statistical Research in Clinical Pathology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: E. K. Harris   Chief, Lab. of Applied Studies   LAS DCRT
OTHER: G. Shakrji   Supv. Systems Analyst   DMB DCRT
          G. Z. Williams   Director, Institute for Health
                              Research, San Francisco, Ca.
          S. S. Brown   Clinical Chemistry Service
                              Clinical Research Centre,
                              Harrow, England

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Applied Studies

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.5	OTHER:

SUMMARY OF WORK (200 words or less - underline keywords)

Three types of statistical time series models have been proposed for the analysis of repeated measurements of blood chemistries or hematologies within an individual. These include a strictly homeostatic model, a nonstationary model which does not presume a homeostatic setpoint, and a more general autoregressive model of which the first two are special cases. All models take into account measurement error in determining the true value at any sampling time. These models are being applied to results from a small sample of presumably normal individuals examined periodically during the last 4 or 5 years. Preliminary results have shown that as expected, all of these models may be used to describe random changes over time in various commonly measured chemistries and hematologies. In some persons, a substance like serum cholesterol will be controlled with sufficient closeness (even over 4 - 5 years) to be represented by the strictly homeostatic model, whereas the same constituent in other individuals will require a nonstationary model to properly account for variations occurring while the individual remains in a healthy status.

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PHS-6040
(12-75)

PHS-NIH
Individual Project Report
July 1, 1975 through June 30, 1976

Project Title: Statistical Research in Clinical Pathology

Previous Serial Number: Same

Principal Investigators: Eugene K. Harris, assisted by
G. Shakarji, DMB, DCRT

Co-Investigators: G. Z. Williams, Institute for Health Research,
San Francisco
S. Brown, Clinical Chemistry Service, Clinical
Research Centre, England

Man Years: Professional 0.5

Project Description:

Background:

The studies of variation in normal blood chemistries which form
the background of this project have been amply discussed in earlier
annual reports. Last year's report discussed the development of
statistical theory to analyze repeated measurements of blood
chemistries or hematologies, for the purpose of detecting statis-
tically significant deviations from an individual's past record.
Three types of statistical models were proposed: 1) a strictly
homeostatic model which presumes the existence of an underlying
setpoint throughout the course of study around which the true
value of the variable (e.g., its concentration) at any given
sampling time may vary; 2) a nonstationary model which does not
presume the existence of such a homeostatic setpoint but does
postulate a random biologic shift from the true value of a
constituent at one sampling time to its value at the next time;
3) a more general autoregressive model, of which the two previous
models represent simplified special cases. This model allows the
possibility of a homeostatic setpoint but permits greater varia-
bility about this setpoint depending on the correlation between
successive biochemical states. All models take into account
measurement error in determining the true value at any given time.
These alternative models have been developed to allow some flexi-
bility in the averaging of past observations from an individual
and forecasting of expected values for comparison with the current
observation. It would be expected for example that electrolytes
might follow a strictly homeostatic model, whereas less closely

controlled quantities such as uric acid, cholesterol, or various
enzymes might be characterized by the more flexible nonstationary
or autoregressive models.

Progress during FY 76:

During the past year, the methodology required to apply these
models to very short time series from individual subjects was
refined, and appropriate computer programs developed. These
methods were then applied to a small sample of presumably normal
individuals examined periodically during the last 4 or 5 years.
The data were made available by Dr. G. Z. Williams of the
Institute for Health Research in San Francisco. Preliminary
results have shown that as expected, all of these models may
be used to describe random changes over time in various commonly
measured chemistries and hematologies. In some persons, a
substance like serum cholesterol will be controlled with
sufficient closeness (even over 4 - 5 years) to be represented
by the strictly homeostatic model, whereas the same constituent
in other individuals will require a nonstationary model to
properly account for variations occurring while the individual
remains in a healthy status.

Last year's annual report discussed the use of a group of programs
for statistical analysis, including components of variance analysis,
trend analysis, tests of normality, etc., applied to studies in
which normal volunteers provided series of weekly blood samples
over a 2 to 3 month interval. These programs have been applied
during FY 76 to data collected under a collaborative study with
the Clinical Chemistry Department of the Clinical Research Centre,
Harrow, England. This study was designed while the principal
investigator was fulfilling a NIH research assignment at the
Clinical Research Centre during 1973-74, but not completed until
the Spring of 1975. The study represents an improvement over
earlier studies in two basic respects: 1) the volunteers were
all seen during the same 2 - 3 month period, eliminating the
problems caused by changes in analytic methods and in laboratory
personnel which often represent confounding factors when small
groups of individuals are studied one after the other; 2) a
long-term analytic variation was eliminated by frozen storage
of samples until the end of the study when all samples were
analyzed together on a large, high-speed multichannel analyzer.
Such analyzers have appeared only recently. They should sub-
stantially improve the signal-to-noise ratio when studies of
intrapersonal variations are undertaken. The analyses of the
data from this study are not quite complete, but indicate that
many constituents show substantially less variation within a
normal individual over time than among individuals, again
providing evidence that conventional population-based normal
ranges are likely to prove inadequate when used to evaluate
changes in an individual's clinical chemistry over time.

Future plans:

   Immediate plans call for extending the application of the time
   series models to a much larger database involving hundreds of
   individuals participating in the biochemical profiling program
   of the Institute for Health Research in San Francisco. It is
   also possible that a similar program, on a much smaller basis,
   will be established by the Clinical Research Centre in England.

Keywords:

   normal variations, inter-intra-individual variation, baseline
   reference values, normal ranges, clinical chemistry.

Publications:

   1. Harris, E.K.: Some theory of reference values I. Strati-
      fied (categorized) normal ranges and a method for following
      an individual's clinical reference values. Clin. Chem.,
      21, 1457, September 1975.

   2. Harris, E.K.: Some theory of reference values. II. Comparison
      of some statistical models of intra-individual variation in
      blood constituents. Clin. Chem., (in press).

   3. Williams, G.Z., Harris, E.K. and Widdowson, G.N.: Comparison
      of estimates of long term analytic variation derived from
      subject samples and controlled serum. Clin. Chem.,
      (submitted for publication).

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities	1. DCRT
2. LABORATORY OF STATISTICAL AND MATHEMATICAL METHODOLOGY	3. James E. Mosimann Chief

I. SUMMARY

Function

The Laboratory of Statistical and Mathematical Methodology (LSM) combines research in mathematical statistics, mathematics, computer and information science, with collaboration and service in these areas to NIH researchers and administrators. There are four sections in LSM:

. The Statistical Software Section (SSS) provides consultation to and collaboration with NIH researchers and administrators in all computational aspects of biomedical data analysis, including selection and support of large program packages. Five specialists in scientific programming are led by a computer systems analyst whose specialty is statistics.

. The Biomathematics and Computer Science Section (BCS), directed by a mathematician, performs independent research and provides consultation and collaboration in the specialties of its six mathematicians and computer scientists.

. The Statistical Methodology Section (SMS) works closely with the Statistical Software Section. Four individuals who work under the direction of a mathematical statistician provide biostatistical consultation and do independent research.

. The Medical Information Science Section (MIS) investigates and develops methods for application of information and computer science to medical language data processing. Five individuals work under the direction of a computer systems analyst who specializes in computational linguistics.

Scope of Work

LSM staff interact with all NIH institutes and with government agencies outside HEW. Fiscal year '75 was LSM's second year as a separate entity within DCRT. The volume of its computational and consultation services expanded considerably over the previous year, and its research activities increased.

Highlights of the Year's Activities

Computation. A very important part of LSM activity is the offering of statistical and mathematical program packages to the NIH user community. LSM accepts responsibility for evaluation of new program packages and their suitability for NIH. When LSM does offer a package to the NIH community, LSM makes three basic commitments:

. The maintenance of the package, with adequate documentation, through NIH computer system changes, package updates and corrections.

. The rapid response to queries concerning user access to a package program including job control language and program parameters.

. The assistance in interpretation of results.

During this year, The Statistical Software Section maintained the following program packages and programs:

BMD,	Biomedical Computer Programs, UCLA
BMDP,	Biomedical Computer Programs, P-series, UCLA
SPSS,	Statistical Package for the Social Sciences, National Opinion Research Center
SAS,	Statistical Analysis System, North Carolina State University
PSTAT,	Princeton Statistical Package, Princeton University
IMSL,	International Mathematical and Statistical Libraries, IMSL Inc.
MSTAT1,	Collection of mathematical and statistical programs, DCRT.

One package formerly offered, the IBM Scientific Subroutines Package, was discontinued this year.

The effort expended in the commitment to maintain these packages is considerable. During this year every package went through at least one update, and totally new documentation for MSTAT1, "the DCRT Mathematical and Statistical Program Manual", was prepared and distributed. The effort expended in response to queries concerning package access is also considerable and requires continuous availability. During the year over 2500 calls were responded to by SSS staff alone. Courses were taught on all the packages except IMSL and MSTAT1.

The use of program packages has shown considerable increase this year over fiscal 75. SAS, whose highest reported use in last year's report was 530 accesses per month, this year averaged 700 accesses per month. SPSS had an average of over 1400 accesses per month. This is the first year LSM has offered this package. There has been a great increase in SPSS use over the past 10 months. (The first month there were 660, the last month 2430 accesses per month.) Routines of the BMD package had an average of 450 accesses per month, a decrease from 600 last year, fiscal 75. However, the new BMDP package absorbed this difference. It had an average of 360 accesses per month, and thus the two BMD packages together averaged over 800. It is anticipated that use of the older BMD package will continue to decline. As an example of a package used for specialized purposes, PSTAT averaged 35 accesses per month,

a three-fold increase over last year's average. The main programs in MSTAT1 average 100 accesses per month. The comparable average for fiscal 75 was 130. (The actual accesses to MSTAT1 include subroutines and main programs and are much larger than these figures.)

The Biomathematics and Computer Science Section itself has developed and maintains two important packages for mathematical modeling by biomedical researchers at NIH. These are MODELAIDE (S/370) and MLAB (PDP-10). Both packages receive wide use at NIH and are distributed internationally. MLAB is one of the most heavily-used programs on the NIH PDP-10. Hundreds of NIH researchers have been able to adapt it to their needs, with only occasional contact with BCS computer specialists. A major improvement in MLAB this year permits efficient solution of a much broader class of ordinary differential equations.

Also under development in BCS is an interactive system of pattern recognition programs. A pilot version of this system is operational on the PDP-10. Courses taught included: MLAB, Pattern Recognition Techniques, and SAIL, a PDP-10 Language. A revision of the manual, "An Introduction to SAIL" was completed this year.

Consultation. The considerable consultative role of LSM is revealed in the list of projects and activities listed in part II of this report.

For the fiscal 75 annual report, a study of LSM consultation revealed the following pattern:

. Mathematical or statistical advice with limited computer use,   20%;
. Mathematical or statistical advice together with considerable use,   40%;
. Computational advice alone,   40%.

This year's pattern is virtually the same for all LSM, excluding MIS. In fiscal 75 about one-third of LSM activity was direct consultation. This year, the volume has increased in all of LSM. MIS does relatively little consulting, all of which falls into the third category listed above.

The amount of time required for LSM consultations varies enormously. Questions posed to LSM staff are often answered by immediate reference to known mathematical and statistical tools, but they may also require many hours of effort and involve new research activities. An illustration is afforded by the LSM collaboration with A. Cheever, Laboratory of Parasitic Diseases, NIAID, in a study of schistosomiasis in Egypt. Schistosomiasis is the condition of being infected by human flatworm parasites of the genus Schistosoma. In Cheever's study there are data for two species, S. haematobium and S. mansoni, which are common parasites of man in Egypt. Counts of worm eggs per gram per organ, various disease conditions, etc., were recorded for 398 consecutive autopsies done in Cairo. Associations of intensity of infection and a variety of disease states were studied. Two sections of LSM are represented in the collaboration. SSS built computer files of the data, edited them, and performed numerous runs with SAS, the Statistical Analysis System. SMS was heavily involved in the selection and interpretation of the statistical

methods which were applied. In fact, some of the statistical methods success-
fully applied to these data were developed within SMS prior to this collabora-
tion. (These are "size-shape" methods, see Project Report ZO1 CT 00013-02).
Two papers with LSM staff as co-authors are in press, and three other papers
are in early draft.

Research. LSM research activities involve many different technical specialties,
including such diverse fields as mathematical statistics, computer science,
linguistics, information science, differential equations, and algebra.

LSM research activities are described in detail in the individual project
reports of part II of this report.

BCS research included projects in computer science, biomathematics, and general
mathematical methods. A BCS staff member was co-author of an extensive survey
article on computers in the research laboratory, published this fiscal year.
Another computer science study detailed a complete set of techniques for
computer manipulation of extendible arrays of data. In biomathematics, research
continued on a formal method of shape description which is natural to .
biological shapes changing by growth and development. During FY75, computer
programs were implemented for analyzing and reconstructing two-dimensional
shapes with respect to the formal descriptions. General mathematical tools
were developed in two areas. For nonlinear differential equations, an existing
method was improved to allow specification of a region in which the solution
is to be sought, and to analyze the resulting error. Another study resulted
in a technique for the analysis of inclusion relations between subspaces of a
vector space. A computer program implementing the method is operational.

In SMS, research on multivariate statistical methods was continued. An SMS
member gave the feature address of a three-day course on principal component
analysis at Louvain, Belgium. Research on practical size-shape multivariate
methods, based on previous theoretical publications (cf. the Fiscal 75 report)
was continued. Practical methods were developed this year and applied to the
analysis of data on the intensity of schistosome infection discussed under
consultation activities.

MIS research activity was mainly concerned with the automatic processing of
natural language medical data. The construction of medical microglossaries
(detailed technical dictionaries for medical specialties) in English, French,
and German was studied. One aspect of these studies was the successful merger
of ICDO (the International Classification of Diseases, Oncology) with SNOP,
the Systematized Nomenclature of Pathology. The purpose of many of the studies
coincides with NCI aims to develop an international data bank for cancers.
The ultimate goal is the development of an information retrieval system which
could be used simultaneously for several (different) languages.

II. LSM PROJECTS AND ACTIVITIES

The following list contains major LSM consulting activities of the year. Then the LSM individual research reports are presented.

Quantitative analysis of interictal behavior in temporal lobe epilepsy. D. Bear, CN, NINCDS. Patients with right or left temporal epileptic foci were contrasted with normal patients and subjects with neuromuscular disorders. Eighteen traits were selected for the evaluation of interictal behavior. These were assessed by two independent true-false questionnaires; one was completed by the subject, the other by a long-time observer of the subject. Computed trait scores for each subject from the true-false questionnaire as well as the original data were analyzed by using analysis of variance, principle components analysis, discriminant analysis, and cluster analysis techniques.

Sleep analysis. W. Duncan, AP, NIMH. The ability of variables observed in sleep analysis to discriminate among four psychiatrically diagnosed patient types was studied. Normal patients, unipolar and bipolar depressives, and insomniacs were subjected to sleep analysis. Discriminant analysis was used to explore sleep data's ability to distinguish the patients.

Schistosomiasis in Egypt. A. Cheever, LPD, NIAID. Of 398 consecutive autopsies performed at Kasr el Ainy Hospital in Cairo, 258 individuals were infected with S. haematobium. Associations of intensity of infection with various disease conditions, cause of death, and other descriptors were studied. Statistical methods used include contingency table analyses, simple and multivariate regression, discriminant analysis as well as size-shape analysis developed within LSM.

Norepinephrine production. C. Lake, M. Ziegler, I. Kopin, LCS, NIMH. The study contrasted norepinephrine production in controls with that in several classes of hypertensives. The investigators' thesis stating that there is no significant difference in norepinephrine production between controls and hypertensives was demonstrated successfully with an analysis of covariance procedure. An analysis of covariance technique was chosen because of intergroup age differences - the hypertensives tended to be older than the controls and this age difference with its concomitant effect on blood pressure, had to be taken into account in any comparison of the groups.

Longevity of females with cystic fibrosis. L. Cohen, PM, NIAMDD. A comparison was made of longevity in females with cystic fibrosis, childbearing vs. non-childbearing. Breslow's generalized Kruskal-Wallis statistic was used to test the significance between the two Kaplan-Meier survivorship functions.

High mortality in female heart surgery patients. T. Spray, IR, OD, NHLI. The mortality incidence subsequent to certain heart surgical procedures is higher for women than for men. Spray's data explored the hypothesis that there may be relatively higher vessel blockage in women than in men. Analyses included t-tests and contingency tables.

Antibody growth in different strains of mice. J. Berzofsky, LCB, NIAMDD. The ability of a proper subset of the genetic loci in antigens to generate

the growth of antibodies in different strains of mice was studied. Three antigen preparations were used in seven species of mice; antibody levels were measured before and at three times after injection of the antibody material. Type II Anova was used to study relative magnitudes of animal and experimental variation in the protocol. Profile analysis was used to assess differences among antigens and among mouse species in antibody production.

Longevity in cancerous mice. W. J. Pendergrast, BC, NCI. The effects of different combinations of surgery, immuno-therapy, and chemo-therapy on the longevity of cancerous mice were studied. Survival curve analysis, using modified Kruskal-Wallis test of Norman Breslow, was used to compare survivorship functions of groups of mice, each subjected to a different treatment sequence.

Selection for body weight in mice. K. Smith, VR, DRS. The primary purpose of this project is to determine if a significant amount of genetic variation remains in highly inbred strains of mice. If it can be established that genetic variation does not exist in these strains, it should be possible to make changes in management procedures used to maintain these strains which would reduce the cost of production. Six strains of mice are included with 72 mating pairs per strain. In each generation there will be approximately 1500 offsprings on which body weight at six-weeks will be measured. The heaviest one-third of the offsprings are selected as parents for the next generation. The statistical procedures used in this study were frequency distributions and analysis of variances.

The amphetamine-induced behavioral syndrome in mice. C. Popper, LCS, NIMH. This project involves the study of the amphetamine-induced behavioral syndrome in mice. It may be expected to have structural features similar to the toxicity produced by amphetamines in man. A full description of behavioral changes produced by a drug requires that different dose levels of the drug be examined, and that changes which occur through time also be considered. Statistical procedures used in this study were correlations, analysis of variance (repeated measures) and cluster analysis.

Abstract motor control in monkeys. E. Schmidt, LNLC, NINCDS. Tests were made of a monkey's ability to match a light on a panel by controlling firing of brain cells in the motor cortex: contact established by implanted electrode. Data are cumulative times spent by the monkey 'at' each of 8 lights while the monkey attempted to match one of them. The analysis focuses on showing that the distribution of times is not uniform, as would be the case if the monkey were uniformly uncoordinated.

Insulin kinetics. P. DeMeyts, CEB, NIAMDD. Insulin-receptor binding is not a simple first-order kinetic reaction. Various methods of describing the apparent cooperativity have been used. With the aid of MLAB, an elegant unified description for this phenomenon has been obtained.

Cluster analysis of grant applications. S. Wright, RAE, DRG. Attempts were made to form clusters of grant applications by various grant descriptors. The shortest spanning path algorithm was used for the cluster analysis.

Bacterial gene expression in mice. M. Geier, LGCB, NIMH. Mice are exposed to stress by toxic or deficient diets. Control groups are contrasted with experimental groups injected with bacterial genes known to degrade the toxic substance or supply the diet deficiency. LSM supplied advice on statistical design of the experiments, performed computer analyses of differential mouse survival rates, and aided in computer generation of graphical displays.

Molecular weight determination. Marc Lewis, LVR, NEI. The ultracentrifuge allows a material to be exposed to a varying gravitational field. By observing the way a compound distributes itself, its molecular weight can be calculated. This involves non-linear curve-fitting and has been done using MLAB for various collections of data obtained by Dr. Lewis.

Models of enzyme kinetics in cells. B. Bunow, LAS, DCRT. A model for the production of product from substrate by enzymes in cells has been developed by Dr. Bunow. This leads to surprising results when studied with appropriate initial conditions. MLAB has been used to evaluate this model numerically.

Blood factor survival in dogs. R. Jaffe, CP, CC. Fibrinogen and platelet survival is measured in dogs, where the same dogs are subjected to different diets. LSM designed a procedure to compute regression lines and halflife intervals, and produced graphical output for display and plotting.

Pharmacokinetics. R. Lutz, R. Dedrick, BEI, DRS. When drugs exhibit long-term binding (e.g., lipid-soluble drugs) the differential equations describing distribution of the drug in the body become stiff, thereby difficult to solve by standard techniques. A special set of programs was written in LSM to solve these equations efficiently with little added work on the part of the user.

Assaying pyrogens in aqueous media. N. Karamian, ES, DRS. A regression analysis with a "pure error" term was used to study a linear predictive model applied for determination of pyrogen concentration in aqueous media. The adequacy of the linear expression was evaluated. Examination of residuals confirmed the experimenter's conclusions concerning a possible curvilinear relation. A special program was written in LSM for this work.

Chemotherapy drug assay. V. Bono, DE, NCI. Tissue culture mouse lymphocytes are subjected to toxic drugs, some known to have chemotherapeutic value in mouse cancer systems. Histograms of DNA content per cell are obtained. LSM designed a mathematical model for histogram data reduction, and performed computer discriminant analyses between therapeutic and non-therapeutic drug groups.

Schizophrenia study. S. Potkin, NIMH. Association between schizophrenia and data recorded in patients' medical/psychological records were under investigation. Extensive detailed assistance was given in defining, loading, editing, and documenting small data base on schizophrenics.

Size distribution of platelets in normal human volunteers. L. Corash, CP, CC. Refinements in obtaining measurements of platelet size have made it possible to study the frequency distribution of platelet diameters, and by conversion, platelet volumes. The assumption of various investigators that this

distribution is lognormal, is not supported by the present data. Although the distribution is positively skewed, and only truncated data are available, chi-squared goodness of fit tests indicate significant departures from lognormality.

Relative potency of two potential carcinogens. L. Keefer, CMT, NCI. Nitrosomorpholine -3, 3, 5, 5-d_4 and nitrosomorpholine were both given to groups of 30 male Sprague-Dawley rats in drinking water at concentrations of 0.35×10^{-3} M and 0.07×10^{-3} M for 30 weeks, and the number of animals bearing liver tumors was recorded for each group. Although the precision of the estimate was impossible to assess because only two doses of each compound was studied, the relative potency of the two compounds was estimated to be at least 5.

Neural synapse response. R. Podolsky, LPB, NIAMDD. The Hodgkins-Huxley equations have been used to model neural response signals in various circumstances. The results show good experimental agreement. This was done using MLAB to obtain the desired graphs.

Metal ion binding for dimethyl amides. K. G. Rao, GRC, NIA. Physical chemistry measurements are made for systems with varying amounts of metal ions at varying temperatures. The effect of the ions on system activation energy is determined. LSM provided advice on mathematical modelling and the use of MLAB to generate graphical displays.

Pathology retrieval system. L. Thomas, LP, NCI. Clinical Center pathology files of autopsy and surgical reports of the last three years were reactivated, and selective retrievals were produced.

Gynecological diagnoses. L. Cousineau, Universite de Sherbrooke, P.Q., Canada. The automatic translation from French to English of the gynecological diagnoses of four Canadian hospitals was accomplished from numerical codes furnished by three hospitals. English equivalents for these codes were automatically produced.

Merger of ICDO and SNOP codes. T. Hanson, CP, NCI. The Systematized Nomenclature of Pathology, SNOP, and the International Classification of Diseases for Oncology, ICDO, were merged, to furnish a new dictionary for the automatic encoding of Clinical Center pathology reports involving cancer. The reports are a part of the records of the Laboratory of Pathology, CC, and this merger is a part of the automatization of their records for use in a computerized hospital information system.

Valve ring abscess in heart surgery. E. Arnett, IR, OD, NHLI. The ability of observable dichotomous pathologies to predict non-observable valve ring abscess in heart surgery patients was studied. Data are multivariate suggesting a discriminant analysis, but on dichotomous [condition either present or absent], as well as continuous variables. Used two-way contingency tables, since task was urgent. Development of a computerized data base for this study is projected. Also planned, with K. Pettigrew of NIMH, is a study of this multivariate discriminant approach.

Asocial Predictors Study. J. Prescott, GD, NICHHD. An attempt is being made to relate several measures of social deprivation to certain measures of social pathology. A file has been created consisting of data for each state over the years 1920, 1930, 1940-72. Variables under study include mortality rates, income and population statistics, alcohol consumption data, and crime statistics. Descriptive statistics and correlation coefficients have been calculated and plotted over time. Some interesting correlational trends have been observed, and these will be pursued subject to further funding.

Copper kinetics in man. E. A. Jones, P. Berk, DD, NIAMDD. Copper kinetics is explored by double labeled experiments in which copper is administered orally and by injection. The two resulting plasma concentration curves must be deconvoluted to determine the rate at which orally administered copper enters the blood stream. A class of models of copper is suggested for which deconvolution is a valid approach. Actual deconvolutions are being computed.

Laser-activated fluorescence counter. J. Wunderlich, S. Sharrow, I, NCI. The laser-activated fluorescence counter is capable of determining the amount of fluorescence within an individual cell, at the rate of 5000 cells per second. Two effects must be removed from the data: 1) the tendency of the instrument to miscount the fluorescence, and 2) the tendency of cells to fluoresce spuriously, beyond the label they have been tagged with. Mathematical techniques for allowing for these two effects are being investigated.

N-channel scintillation counter. L. Kohn, CPB, NIAMDD; R. Tate, CSL, DCRT. A technique for minimizing the error in 2-channel scintillation counter has been extended to the N-channel case. This technique will be tried on real data to confirm its effectiveness.

Effectiveness of epilepsy drugs. R. Krall, ANR, NINCDS. Causes of activity of epilepsy drugs are being studied using pattern recognition programs developed at LSM. Features (variables) are various characteristics of compounds (e.g., molecular weight, solubility) as well as test results (e.g., ED50). Attempts are being made to determine which features are important to predict the effectiveness of a new drug.

III. PUBLICATIONS

Cheever, A. W., Elwi, A. M., Kamel, I. A., Mosimann, J. E. and Danner, R. N.:
Intensity of infection as related to pathological lesions in Bilharzial
patients. Proc. of the Internat'l Conf. on Schistosomiasis, Cairo, Egypt,
(in press).

Darvey, I. G., Shrager, R. I. and Kohn, L. D.: Integrated steady state rate
equations and the determination of individual rate constants. J. Biol. Chem.
250, 4696-4701, 1975.

Graepel, P. H., Hanson, D. E. and Pratt, A. W.: Comments on the use of the
systematized nomenclature of pathology. Methods of Information in Medicine,
Vol. 14, No. 2, 1975.

Graitson, M.: Identification et transformation automatique des morphemes
terminaux dans le lexique medical francais, Cahiers de Lexicologie, Vol. 26,
No. 1, 1975.

Graitson, M. and Dunham, G.: Traitement automatique de francais medical,
Cahiers de Lexicologie, 1976 (in press).

Hutchinson, G.: Embedding and unsolvability theorems for modular lattices,
Algebra Universalis, (in press).

Pacak, M. G., Pratt, A. W. and White, W. C.: Automated morphosyntactic
analysis of medical language, Information Processing and Management, Vol. 12,
pp. 71-77, 1976.

Sadigursky, M., Kamel, I. A., Elwi, A. M., Danner, R. N., Cheever, A. W. and
Andrade, Z. A.: Absence of schistosomal glomerulopathy in Schistosoma
haematobium infection in man. Transactions of the Royal Society of Tropical
Medicine and Hygiene, (in press).

PERIOD COVERED

Ju1y 1, 1975 through June 30, 1976

TITLE OF PROJECT (80 characters or less)

Automated Data Processing of Medical Language

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. G. Pacak	Computer Systems Analyst	LSM DCRT
	A. W. Pratt	Director	DCRT
OTHER:	P. Graepel	Expert	NCI
	G. Dunham	Computer Programmer	LSM DCRT
	S. A. Harper	Computer Programmer	LSM DCRT
	M. DeMeyts-Graitson	Guest Worker	LSM DCRT

COOPERATING UNITS (if any)

Department of Pathology, CC

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Medical Information Science Section

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS: 2.5	PROFESSIONAL: 2.5	OTHER: 0.0

SUMMARY OF WORK (200 words or less - underline keywords)

We have continued to improve the efficiency of the program for information storage and retrieval of pathology data which is being used by the Department of Pathology, NIH. A similar program was developed for automated encoding of French pathology data in cooperation with the Clinical Center of the University of Sherbrooke, Sherbrooke, Quebec, Canada.

The major objective of the project is the design of a sophisticated system for automated processing of medical language in general, and the design of a formal model for the semantic interpretation of medical records.

Project No. Z01 CT 00001-05 LSM
1. Lab. of Stat. and Math.
   Methodology
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1975 through June 30, 1976

Project Title: Automated Processing of Medical Language

Previous Serial Number: 4.9

Principal Investigators: M. G. Pacak, A. W. Pratt

Other Investigators: P. Graepel, G. Dunham, S. Harper,
                      M. DeMeyts-Graitson

Man Years:
            Total: 2.5
            Professional: 2.5
            Other: 0.0

Summary of Work:

   We have continued to improve the efficiency of the program for information
   storage and retrieval of pathology data which is being used by the
   Department of Pathology, NIH. A similar program was developed for
   automated encoding of French pathology data in cooperation with the
   Clinical Center of the University of Sherbrooke, Sherbrooke, Quebec, Canada.

   The major objective of the project is the design of a sophisticated system
   for automated processing of medical language in general, and the design of
   a formal model for the semantic interpretation of medical records.

Project Description:

   For the past several years, an effort has been underway to design and
   develop a system for automated indexing and retrieval of pathology data.
   The system which became operational in 1971 includes the acquisition of
   textual information, the interrogation of the SNOP dictionary (Systematized
   Nomenclature of Pathology), a set of morphosyntactic transformation rules
   and a set of syntactic-semantic rules to allow for the identification of
   the information content of the input messages. The textual information
   consists of diagnostic statements which represent the pathologist's summary
   of disease and its manifestation.

   In connection with further improvements of the encoder the work was
   continued on the development of procedures for the construction of medical
   microglossaries for cardiology and oncology to be used in computer
   processing of medical language. A man-machine interactive lexical refine-
   ment algorithm is under development in this direction.

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A program was developed for the identification and transformation of terminal morphemes in French (M. Graitson) which is a part of the French encoder of medical diagnoses. This program for automated encoding of French pathology data was developed in cooperation with the Clinical Center of the University of Sherbrooke, Canada. It is fully compatible with the NIH English encoder.

We have attempted to prepare a set of paraphrasing rules which are based on the definition and formalization of semantic relationships among semantic constituents forming the compound words derived from Greek and Latin. We have analyzed the word forms which end in -ITIS (inflammation process) and will test the paraphrasing rules on larger medical context. Similar rules will be developed for French compound word forms ending in -ITE.

The development of paraphrasing rules will increase significantly the interpretive power of medical lexicon and make it possible to interpret synonymous phrases which are not contained in the dictionary but which occur in the medical text.

Future Efforts:

a) Further development of the SNOP-based metalanguage will depend on the definition of semantic relations between the SNOP T, M, E, F categories and relations existing among complete TMEF statements. But the definition of implicit and explicit relations between clusters of complete TMEF statements represents a difficult task.

b) Improvements of morphosemantic segmentation and paraphrasing rules for medical compound words as a part of the study of the structure of medical microglossaries.

c) Application of statistical (quantitative) linguistics to medical data processing, analysis of medical style and the construction of medical dictionaries.

Publications:

Pacak, M. G., Pratt, A. W., White, W. C.: Automated Morphosyntactic Analysis of Medical Language, Information Processing and Management, Vol. 12, pp. 71-77, 1976.

Graitson, M.: Identification et transformation automatique des morphemes terminaux dans le lexique medical francais, Cahiers de Lexicologie, Vol. 26, No. 1, 1975.

Graitson, M., Dunham, G.: Traitement automatique de francais medical, in press, Cahiers de Lexicologie, 1976.

PERIOD COVERED

July 1, 1975 through June 30, 1976

TITLE OF PROJECT (80 characters or less)

Pattern Recognition

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. B. Shapiro	Research Mathematician	LSM DCRT
OTHER:	R. Krall	Staff Associate	ANR NINCDS
	R. S. Wright	Health Scientist Admin.	RAE RG
	G. D. Knott	Computer Specialist	LSM DCRT
	A. Schultz	Supervisory Elec. Engineer	CSL DCRT
	W. Jennings		LPB NIAMDD

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Biomathematics and Computer Science Section

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS: 2.0	PROFESSIONAL: 2.0	OTHER: 0.0

SUMMARY OF WORK (200 words or less - underline keywords)

Computer pattern recognition techniques have been developed for general use and have been applied to a variety of problem areas. The first version of a display-oriented pattern recognition program for the DEC-10 computer has been completed. It includes algorithms for feature selection, feature reduction, and cluster analysis. The package now includes ten algorithms, and about 20 more will be added in the coming year. An improved algorithm for nearest neighbor classification, one of the most successful techniques for pattern classification, has been developed. Cluster analysis techniques have been applied to a variety of data, including compounds used to treat epilepsy, in an attempt to determine which chemical properties of the drugs are important in making them effective, and grants data, to look for relationships among the many disciplines receiving NIH grants. A study of laboratory automation, which includes some of the pattern recognition methods used for laboratory data, has been completed.

PHS-NIH
Individual Project Report
July 1, 1975 through June 30, 1976

Project Title: Pattern Recognition

Previous Serial Number: Same

Principal Investigator: Marvin B. Shapiro

Other Investigators: Ronald Krall, Stuart Wright,
                       Gary Knott, Arthur Schultz,
                       William Jennings

Cooperating Units: ANR, NINCDS; RAE, RG; CSL, DCRT; LPB, NIAMDD

Man Years:
          Total: 2.0
          Professional: 2.0
          Other: 0.0

Project Description:

  Objectives:

    The main objective is to provide an easy-to-use package of pattern
    recognition programs for the use of NIH researchers.

  Methods:

    A large number of the most recent and well-proven pattern recognition
    algorithms have already been incorporated into independent programs.
    These programs are being put together into one large system of programs
    which is based on the MLAB system and used similarly.

  Significance to Biomedical Research:

    Pattern recognition techniques are now widely used in many disciplines
    and they are being increasingly used in biomedical research problems.
    This system of programs will give researchers easy access to the most
    important pattern recognition techniques and algorithms.

  Proposed Course:

    At present, eight algorithms have been incorporated into the package,
    including techniques for feature reduction and cluster analysis. It
    is planned to add more cluster analysis techniques - including graphs of
    minimal spanning trees and dendrograms - and learning machine algorithms

including decision learning trees and other methods for pattern classification. A manual will be prepared and distributed, and classes will be taught.

Publications:

Shapiro, M. B.: The choice of reference points in best-match file searching. Comm. Assoc. Computing Machinery, 19, 6, 1976.

Shapiro, M. B., Schultz, A. R. and Jennings, W. H.: Computers in the research laboratory. Ann. Rev. Biophys. Bioeng. 5, 177-204, 1976.

PERIOD COVERED
July 1, 1975 through June 30, 1976

TITLE OF PROJECT (80 characters or less)

Research Topics in Computer Science

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. D. Knott   Computer Specialist   LSM DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Biomathematics and Computer Science Section

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.5	0.2

SUMMARY OF WORK (200 words or less - underline keywords)

Various storage and retrieval algorithms have been studied. The development of flexible and efficient storage and retrieval algorithms is very useful, since such algorithms are used in almost all computer programs. Thus biomedical computation in particular can benefit from improved storage and retrieval methods.

Currently, an exhaustive survey of storage and retrieval methods is underway. This includes the recently introduced k-d tree method.

Optimal item orderings in split hashing schemes and certain interesting algebraic characterizations of fixed permutation open addressing methods are also being studied currently.

Project No. <u>Z01 CT 00009-02 LSM</u>
1. Lab. of Stat. and Math.
   Methodology
2. Not Applicable
3. Bethesda

PHS-NIH
Individual Project Report
July 1, 1975 through June 30, 1976

Project Title: Research Topics in Computer Science

Previous Serial Number: Same

Principal Investigator: Gary D. Knott

Other Investigators: None

Cooperating Units: None

Man Years:
          Total: 0.7
          Professional: 0.5
          Other: 0.2

Project Description:

The object of this project is to develop theoretical bases for new computer methods which will expand and improve the use of computing in biomedical computation. The methods used are the application of known algorithms and the development of new pertinent theorems involving combinatoric and other related mathematics. Research work in storage and retrieval algorithms and their efficiency has been the primary topic of concern.

Currently, an exhaustive survey of storage and retrieval methods is underway. This includes the recently introduced k-d tree method. Various improvements and refinements in both the algorithms, and their analysis, are being studied.

Optimal item orderings in split hashing schemes and certain interesting algebraic characterizations of fixed permutation open addressing methods are also being studied currently.

Several publications cited below reflect work done within this project.

Publications:

Knott, Gary D.: "A Numbering System for Permutations of Combinations", Communications of the ACM, Vol. 19, No. 6, pp. 355-356, June 1976.

Ketelslegers, Jean-Marie, Knott, Gary D., Catt, Kevin J.: "Kinetics of Gonadotropin Binding by Receptors of the Rat Testis: Analysis with Non-Linear Curve-Fitting", to appear in Biochemistry, 1976.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00010-02 LSM

PERIOD COVERED
Jul. 1, 1975 through June 30, 1976

TITLE OF PROJECT (80 characters or less)

Nonlinear Equations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. I. Shrager	Mathematician	LSM DCRT
OTHER:	G. D. Knott	Computer Specialist	LSM DCRT
	E. Hill	Mathematician	LAS DCRT
	J. E. Fletcher	Research Mathematician	LAS DCRT

COOPERATING UNITS (if any)

LAS, DCRT

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER: 0.0

SUMMARY OF WORK (200 words or less - underline keywords)

Methods are developed for solving nonlinear equations frequently encountered at NIH, usually in the context of constrained nonlinear least squares or in the solution to nonlinear differential equations. Related problems, such as asymptotic error analysis, and the efficient treatment of sparse systems, are also considered.

PHS-NIH
Individual Project Report
July 1, 1975 through June 30, 1976

Project Title: Nonlinear Equations

Previous Serial Number: Same

Principal Investigator: Richard I. Shrager

Other Investigators: Gary Knott
                      Edward Hill
                      John Fletcher

Cooperating Units: LAS, DCRT

Man Years:
            Total: 1.0
            Professional: 1.0
            Other: 0.0

Project Description:

    Objectives:

        To develop methods for solving nonlinear equations frequently encountered
        at NIH.

    Methods:

        A continuing effort is made to create methods or extend existing methods
        to solve problems in a host of NIH applications, and to house those
        methods in accessible computer programs or routines. Modelaide and MLAB
        are two examples.

    Major Findings:

        Marquardt's method for nonlinear least squares was extended to handle
        linear constraints. A suitable error analysis was devised for
        constrained parameters. A method for solving nonlinear stiff
        differential equations was adapted from a Ph.D. thesis of Kai-Wen Tu.
        Marquardt's method, see a), is now being extended to norms other than
        least squares. Preliminary results are promising.

    Significance to Biomedical Research:

        These methods are now being applied to problems in human metabolism, cell
        growth, chemical kinetics, and spectral analysis (UV, IR, CD, ORD, NMR,
        ESR).

Proposed Course:

As the methods are proved in test and practice, they will be incorporated into easy-to-use systems like MLAB, and as a result, the systems themselves should evolve to do more useful work with less human and machine effort.

Publications:

Darvey, I. G., Shrager, R., and Kohn, L. D.: Integrated Steady State Rate Equations and the Determination of Individual Rate Constants. <u>J. Biol. Chem.</u> 250, 4696-4701, 1975.

PERIOD COVERED

July 1, 1975 through June 30, 1976

TITLE OF PROJECT (80 characters or less)

Discrete Mathematics and Applications

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. A. Hutchinson   Research Mathematician   LSM DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Biomathematics and Computer Science Section

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0.0

SUMMARY OF WORK (200 words or less - underline keywords)

Work continued on linear programming methods for the analysis of chemical reaction systems.

A computer method was developed for solving an open problem of the theory of vector spaces, specifically concerning lattice word problems for the study of inclusion relations between subspaces of a vector space.

Project Title: Discrete Mathematics and Applications

Previous Serial Number: Same

Principal Investigator: George Hutchinson

Other Investigators: None

Cooperating Units: None

Man Years:
            Total: 0.5
            Professional: 0.5
            Other: 0.0

Project Description:

   Objectives:

      The project objective is to develop mathematical theory and computational
      techniques using discrete mathematics (algebra, combinatorics and graph
      theory), and to apply such methods to appropriate problems of biomedical
      research and computer science.

   Methods Employed and Major Findings:

      Part of the earlier work on this project was a study of exhaustion of
      reactants in chemical reaction systems. A linear programming method
      to obtain quantitative estimates for this problem had been developed.
      In this fiscal year, computer analyses of specific reaction systems
      were made, using this method. Applications to systems for producing
      chemical and biological substances were explored.

      A computer method was devised and implemented for solving an open
      problem of the theory of vector spaces. The study concerns inclusion
      relations between the subspaces of a vector space, and the related
      intersection and spanning operations, called the "lattice" operations.
      (In a three-dimensional vector space, for example, two planes containing
      the origin intersect in a straight line, and two straight lines passing
      through the origin span a unique plane.) Using the method, any formula
      which is an inclusion or equality relation between expressions involving
      intersection and spanning operations can be analyzed. The analysis
      determines whether or not a given formula of this type is a "law" for

the theory of vector spaces, that is whether or not it is true in all cases. Technically, the method is said to solve the "word problem" for lattices of subspaces of vector spaces.

Significance to Biomedical Research and the Program of the Division:

General purpose mathematical techniques and computer programs implementing them are made available to the biomedical research community.

Proposed Course:

Computer programs will be documented and made available for installation at other computer sites. Applications using vector space techniques will be examined for problems for which the new method yields helpful information.

Publications:

Hutchinson, G.: On the Representation of Lattices by Modules. Trans. Amer. Math. Soc. 209, 311-351, 1975.

Hutchinson, G.: Embedding and Unsolvability Theorems for Modular Lattices. Algebra Universalis, in press.

PERIOD COVERED

July 1, 1975 through June 30, 1976

TITLE OF PROJECT (80 characters or less)

Biological and Visual Shape

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: H. Blum   Res. Gen. Phys. Scientist   LSM DCRT
OTHER: R. L. Webber   Chief, Clin. Invest. Branch CIB NIDR
       R. Nagel   Senior Staff Fellow   CIB NIDR

COOPERATING UNITS (if any)

DMG, CIB, NIDR

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Biomathematics and Computer Science Section

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS: 0.9	PROFESSIONAL: 0.9	OTHER: 0.0

SUMMARY OF WORK (200 words or less - underline keywords)

This project develops and applied a new geometry of biological shape that gives a natural and efficient description to a variety of biological objects at vastly differing levels: chromosomes, cells, organs, organisms.

One application is to automation of shape analysis for diagnosis and taxonomy. A second is to the psychology and neurophysiology of shape processes in vision. A third is to the description and understanding of organ and organismic development.

This year, a computer program that does the required process on 2-dimensional outline objects has been completed. Preliminary analysis of some objects has been carried out by hand.

Future work includes extension to 3-dimensions and gray scale data (pictures). Application will be made to both biological description and development, and to the visual process.

PHS-6040

PHS-NIH
Individual Project Report
July 1, 1975 through June 30, 1976

Project Title: Biological and Visual Shape

Previous Serial Number: Same

Principal Investigator: Harry Blum

Other Investigators: R. L. Webber, R. Nagel

Cooperating Units: DMG, CIB, NIDR

Man Years:
            Total: 0.9
            Professional: 0.9
            Other: 0.0

Project Description:

The overall objective of this project is to develop a formal descriptive language natural to biological shapes and apply this language to the variety of problems arising in main areas of biology and medicine: taxonomy, neurobiology and organismic development. This would permit a better modeling and understanding of these processes and also allow for the automation of many shape processes now done by humans.

The methods employed stem primarily from a new geometry based on growth as the primitive process, and conceived by the principal investigator. It is applied to a variety of problems, both to clarify the biological processes taking place and to develop the mathematics in new biologically relevant directions. These include cell and tissue description from light microscopy, skeletal descriptions of growing organisms, chromosome description, visual psychophysics and visual neurophysiology.

The major accomplishment this year is the development of a computer program for performing the necessary geometric processes on 2-dimensional outline figures and for reconstructing the objects from the new type of description. The program allows quanticized description on a grid to yield smooth properties and for smooth objects to be reconstructed. The program has been written to be capable of being a general facility at NIH and elsewhere, as well as for continued use on this project. There is a collaboration in this work which is desired under project ZO1 DE 00158-02 CIA.

Publications: None

PERIOD COVERED
Ju'y 1, 1975 through June 30, 1976

TITLE OF PROJECT (80 characters or less)

Multivariate Statistical Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. E. Mosimann   Chief   LSM DCRT
OTHER: R. N. Danner   Computer Systems Analyst   LSM DCRT
        C. B. Clark   Computer Specialist   LSM DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Office of the Chief, LSM, DCRT

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER: 0.0

SUMMARY OF WORK (200 words or less - underline keywords)

Multivariate statistical methods, (size-shape methods) for analyzing ratios which follow a lognormal distribution have been developed. These size-shape tests have been applied to data on number of schistosome eggs/organ in man at autopsy as well as morphological data on birds. Computer programs from standard packages SAS, SPSS, have been adapted to give the desired tests.

PHS-NIH
Individual Project Report
July 1, 1975 through June 30, 1976

Project Title: Multivariate Statistical Methods

Previous Serial Number: Same

Principal Investigator: James E. Mosimann

Other Investigators: Ray N. Danner
                      Cecelia B. Clark

Cooperating Units: None

Man Years:
        Total: 1.0
        Professional: 1.0
        Others: 0.0

Project Description:

The overall objective of this project is the study of multivariate
statistical methods for the analysis of data which take the form of ratios
or proportions. During this past year statistical tests have been
developed and applied to data which include the distribution of schistosome
eggs by organ at autopsy, data of A. Cheever, NIAID, and morphological
measurements of birds, F. James, NSF. Exact small-sample statistical
methods are used in these analyses. As a result of work reported under
this project last year (Project Z01 CT 00013-01) Mosimann has been invited
by the Commonwealth Scientific and Industrial Research Organization, CSIRO,
of Australia under their international visitors program in mathematical
statistics.

Publications: None

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities   1. DCRT

2. COMPUTER SYSTEMS LABORATORY   3. Alan M. Demmerle
                                                     Chief

I. SUMMARY

Function

The Computer Systems Laboratory (CSL) identifies and solves problems in areas
of biomedical research and clinical care where real-time data collection,
analysis, display and experiment control are required, where economic consid-
erations favor a small computer or where proximity of the computing equipment
to the work site is important to successful solution.

The activities of CSL's electronic engineers and computer scientists center
in four principal areas:

  computer applications in clinical projects

  computer applications in laboratory research

  other types of computer research relating to biomedical applications

  consultation with researchers in need of computer expertise.

CSL's methods of approaching projects in these several categories are as
varied as the applications themselves, because each problem presents unique
challenges. Sometimes the objectives of a project are clearly defined. The
investigator knows exactly what he wants automation to achieve. In this
case, the path to solution of the problem is conceptually straight forward,
even though it is often time-consuming and technically difficult. In
projects of this kind, CSL staff analyze the user's specific requirements,
evaluate various alternative solutions with regard to technical merit, time
to completion and cost. The hardware and software aspects of the system
which best meet the user's needs are then specified.

A different approach is required when an investigator believes his research
will benefit from automation but does not know how to take full advantage of
the possibilities. In projects of this kind, CSL staff must become more
intimately involved with the research in order to discover how automation
can be achieved and how research methods need to be altered to utilize this
technology.

Whenever possible, hardware and software components of the recommended systems
are purchased from commercial sources. When components that meet the user's
needs are not commercially available, they are developed by CSL engineering

and programming staff and are refined to the point that they become functioning, integrated parts of the user's research. Since users' requirements often change as their research progresses, collaboration between the users and CSL staff continues beyond initial implementation of a system so that necessary adaptations can be made.

Because the costs of computer hardware have decreased, it is now economically feasible to develop small dedicated systems rather than larger systems concurrently shared among several investigators and instruments. This reduces the overall complexity of the systems.

Scope of Work

This year CSL's 33 person staff worked on some two dozen projects involving laboratory and clinical research in seven other NIH institutes and divisions. Preliminary discussions were held regarding several other projects. Most CSL projects relate to intramural research but some extramural consultation is provided. CSL staff advise NIH groups that fund grants or contracts involving computer systems and computing applications.

Highlights of the Year's Activities

Computer Support for Clinical Care

Computers provide physicians with valuable tools in decision-making in the clinical care of patients. They also free highly trained medical personnel from routine functions so that they are able to devote more of their time to direct patient care. The full role of computer technology in clinical medicine is still evolving, and CSL is becoming increasingly involved in the use of small-computer support of clinical care and research. During the past year, two exciting new projects have been begun.

NCI Radiation Therapy. CSL is working with the Radiation Oncology Branch of the National Cancer Institute on a project to take advantage of recent advances in computerized axial tomography (CAT) to achieve more accurate planning and delivery of x-ray therapy. Computer support for radiation therapy planning is widely utilized but its effectiveness has been limited by the difficulty of pinpointing the locations and x-ray absorption characteristics of tissues, tumors and organs in specific patients. Recently a British firm, EMI, has developed a whole-body scanner that produces cross-sectional body images that provide this type of information. The Radiation Oncology Branch has purchased an EMI scanner and intends to use the output from the scanner's computer as data for computation of radio therapy plans.

CSL involvement, in the near term, is directed toward selecting a computer system with three dimensional capability which is appropriate for planning radiation therapy, implementing an efficient scheme for transferring EMI scans to the selected system, developing an interactive multi-intensity display facility capable of providing the radiologist with varied visual representations of body scans, and producing a versatile mechanism for computer entry of important anatomical and tumor contours. Long range CSL goals include mathematical optimization of the sophisticated dosimetry plans thus developed and automation of patient setup and dose delivery.

During the six months since the project began, a state-of-the-art review of radiation threatment planning hardware and software has been conducted. CSL recommendations to the Radiation Oncology Branch, favoring procurement of a DEC PDP-11/70 computer system and AECL treatment planning software are being implemented.

NCI Intensive Care Unit Support. CSL is working with the Surgery Branch of NCI to develop computer-aided monitoring for two operating rooms and the NCI post-surgical recovery rooms in the Clinical Center, with particular emphasis on respiratory monitoring. Computerization of intensive care units provide many advantages, including rapid display of trends in both tabular and graphic forms, alarm signaling when vital signs deviate from predetermined limits, immediate access to information on acid-base and cardiac output, data logging and reporting mechanisms which relieve nursing staff of clerical functions, and establishment of a manageable data base for current and future research. However, the impetus and principal justification for installing a computer in the NCI intensive care unit is its capacity for respiratory monitoring.

During the past six months, in conjunction with NCI surgeons, CSL studied care unit requirements. Specific respiratory monitoring goals were defined. Current respiratory monitoring equipment and practice were analyzed to determine their effectiveness as indicators of physiologic change and failure of life support systems. Methods and required accuracy of respiration monitoring in the operating room were examined, flow computational requirements were evaluated and the economic and performance characteristics of equipment such as mass spectrometers and gas analyzers were assessed.

The Request for Proposals generated by CSL is nearing completion. If NCI's plans to expand its recovery room facilities proceed according to schedule, a standard monitoring system could be installed and operational by the end of the year. However, commercially available systems do not include respiratory monitoring functions. Therefore, in addition to developing the necessary software and hardware interfaces for the system, CSL will add the required respiratory monitoring capability. This should lag behind installation of the general system by no more than nine months.

Ongoing Clinical Projects. The NHLI Intensive Care Unit System designed by CSL differs considerably from the projected NCI system. Designed primarily to meet the NHLI's research requirements, the system provides continuous monitoring of ECG, arterial pressure, venous pressure, temperature, blood loss and urine output signals. Unlike commercial systems which cycle among a number of beds and capture only a fraction of the available data, the NHLI system monitors four beds simultaneously. This versatile, easy-to-use system can be modified to meet the demands of changing protocols. CSL's recent work on it has concentrated on production of a cardiac output analysis program, "HELP" programs to assist users and more elaborate preprocessors for ECG and pressure waveforms.

NHLI Catheterization Laboratories On-Line Computer System. Last year, in response to a request from NHLI's Cardiology Branch, CSL conducted a state-of-the-art study of methods for catheterization laboratory computerization.

Further studies this year in areas of specific concern to the Cardiology
Branch revealed that computerization offers limited advantage, in catheter-
ization laboratory decision-making processes, over manual methods. However,
the accuracy, consistency and manageability of data collection and compu-
tation surpasses hand calculation techniques to such an extent that an on-line
system is virtually essential to future off-line research.

Most institutions give a reduction in patient recall as the principal justi-
fication for automation. Since this is not a major problem at the NIH, the
future of the project rests primarily on the priority attached by the
Cardiology Branch to long-term off-line research. Procurement of an on-line
computer system has been held in abeyance pending completion of a Cardiology
Branch program review.

Smaller Clinical Projects. CSL performed limited work on several smaller
projects including a system for collection and analysis of data in the NHLI
Pulmonary Laboratory and a system for playback and analysis of tape recorded
ECG signals obtained from ambulatory heart patients.

Computer Support for Laboratory Research

NCI Fluorescence Activated Cell Sorter. This project, begun last year, became
operational and was expanded during FY-76. It involves collection, analysis
and display of data from two different types of cell sorters. Dr. John R.
Wunderlich of the Immunology Branch of NCI uses a sorter which separates
cells according to their optical properties. A PDP-11 computer system monitors
this process, collects data on light scatter which relates to cell size and
fluorescence data and formats and transmits this information to the DCRT PDP-
10 facility for complex analysis. The results are then sent back to the PDP-
11 for three dimensional graphic display. Currently, CSL is adding the
capability to process a second fluorescence signal from Dr. Wunderlich's
sorter.

CSL is also expanding the system to include collection of data from the cell
sorter used by Dr. Chester J. Herman of the NCI Laboratoy of Pathology.
Although this sorter is of a different type and is located two floors away
in the Clinical Center, data from the two sorters will be collected simulta-
neously. Analysis and display will be handled for one instrument at a time.

This system provides a versatile but economical solution to analysis and
display problems for this type of research. The portions of it dealing with
the collection, analysis and display of data from Dr. Wunderlich's sorter
are to be copied for use by Dr. E. Scher in the Naval Medical Center facilities
in Bethesda.

Microcomputer Monitored Spectroscopy. This year CSL produced its first labor-
atory automation system using a microcomputer, a relatively new innovation in
the field of electronics. Because of its small size and low cost, this system
makes it possible to apply computer control technology for purposes not cost-
effective when mini-computers are used. This system, which belongs to Dr.
Hendler in the Laboratory of Cell Biology of NHLI, controls spectrophotometric
measurements in cytochrome studies.

The microcomputer controls the rate of oxidation and reduction of a solution containing a mixture of cytochromes, by controlling the direction and magnitude of current through a set of generating electrodes while monitoring the potential of the solution via measuring electrodes and recording optical density and wavelength. The key to the success of this approach lies in the ability of the microprocessor to dynamically compare the potential of the two electrode systems and depolarize the generating electrodes relative to the solutions potential. This degree of control was not possible in previous studies using conventional techniques. Electrical potential, optical density and wavelength data are formatted and transmitted by telephone link to the DCRT PDP-10 for curve fitting and other analysis. The results are then transmitted back to Dr. Hendler's laboratory. The PDP-10 also stores various programs used by the microcomputer and down loads them as needed by the same communication path.

This system provides computer capability for on-line laboratory process control and data acquisition at a minimal cost, but can use the resources of the central PDP-10 for programming, complex calculation, and long term data and program storage.

Mass Spectrometer Data Collection and Analysis. Work done several years ago by CSL in mass spectrometer data collection and analysis has provided useful background for automation of NIMH's LKB 9000 gas chromatograph/magnetic deflection mass spectrometer. In a project begun this year, CSL has undertaken to automate data collection and analysis and focus the mass spectrometer which is the work horse in the Clinical Science Laboratory of NIMH. The system will be built around the LKB 9000 and a PDP-11/10 computer. CSL's work centers on automating a subset of the normal operating procedure to allow the spectrometer to be used as a quantitative rather than a qualitative instrument.

Installation of a New Hybrid Computer System. Because of the acute demand for space in Building 10, CSL has dismantled and surplused the large Hybrid Computer purchased about 11 years ago as a general utility for the NIH research community, replacing it with more modern and compact equipment. The new system, built around a PDP-11/10, provides a facility for general purpose data acquisition, A/D conversion, plotting and display. It became operational at the end of this reporting period.

Other Computer Research Related to Biomedical Applications

While the bulk of CSL's work is directly related to clinical care and laboratory automation, considerable effort is also devoted to such areas of computer research as medical telecommunications and automation of library transactions.

The NIH Library Project. CSL continued its work on the computer system designed to automate collection and maintenance of daily transactions in the NIH Library. This system, which covers charging, discharging, and reserving of library materials, is based on a computer to be located in the library along with optical scanning devices, a CRT terminal and other specialized input devices. Periodically the data collected will be transferred to master

files of library holdings and patrons in the DCRT central facility.

Initially CSL intended to adapt for NIH use a system developed at the University of South Carolina. However, there are so many differences in management and operation of the two libraries that a significant amount of redesign and reprogramming was necessary. The NIH system is to be operational in July 1976 with the expectation that minor modifications will be made during the summer. Development of a portable terminal to keep track of reference materials used within the library is also planned. The NIH system has already attracted considerable attention from other libraries, so it is likely that the results of CSL's developmental effort will be applied elsewhere.

The Medical Telecommunications Project. This CSL project, started several years ago, involves development of a technology to make computer services available by using an ordinary touch-tone telephone as a computer terminal. Two years ago, a prototype system was completed that uses the telephone pushbuttons to provide input to the computer, which replies in voice over the telephone. To illustrate the potential usefulness of this system, CSL developed six medical applications programs.

During FY-76, CSL's efforts have been directed toward making the speech generation more economical. A voice synthesizer has been interfaced to a microcomputer which converts English text to phonetic codes that can be enunciated by the synthesizer. This compact combination of equipment can be used to add touch-tone and voice response capability to almost any time-share computer system. It has many possible applications in the health care industry and elsewhere. CSL has received inquiries about this economical device from both Federal agencies and private industry. A Veterans Administration contractor who is developing a reading machine for the blind has based his system on CSL's design. From an input derived from an optical character reader, the contractor has been able to produce an intelligible voiced reproduction of printed material.

Consultation

In addition to the work described above, CSL consults with researchers in need of computer expertise. This consultation can take the form of simply providing advice on a specific problem or can result in the design of special purpose hardware or in writing of special purpose software. Several such projects were undertaken for intramural programs. They typically require 3-6 man months of work. Recently several of these projects have involved "programmable calculators". These calculators provide a relatively new concept in the small computer market, and because of their size and ease of programming provide an economical basis for an increasing number of laboratory automation projects.

Future Plans

Over the past 10 years CSL has worked with nearly all the NIH institutes on a wide variety of projects. Some have been quickly concluded. Others have required several years from the initial functional analysis through design,

development, installation and continuing collaboration with users to adapt the systems as research requirements evolve. In some cases the nature of CSL participation changes. For example, having helped to develop a computer system for therapy planning, CSL may move into application of this planning capability by helping to automate patient setup and dosage delivery.

CSL involvement in developing small-computer support for clinical care and laboratory research programs continued during FY-76. Minicomputers, micro-computers and small programmable calculators have all been used. Use of the central DCRT PDP-10 computer to support these small computers has grown. This represents the maturing of a concept toward which DCRT has been working for some time: an interactive computer network in which the versatility and usefulness of small computers in laboratories are expanded through wire connection with the computing power of a large central facility. CSL anticipates that wider use of this system will provide not only an economical computer capability for on-line laboratory process control and data acquis-ition but better long-term data storage and retrieval capability as well.

In its consultancy role, CSL expects to continue its services to intramural programs and expand its services to NIH collaborative and extramural programs. Intramural consultation often includes development of hardware and software systems. Extramural consultation activities are expected to remain primarily advisory in the areas of automated data collection, display and analysis, data transmission, certain aspects of biomedical sensor design and all aspects of real-time computer design.

To continue its present range of activites and respond to these new challenges, CSL plans to maintain a staff which has both a proven breadth of experience and competence in system development and expertise in new digital equipment and techniques.

LEVEL OF EFFORT AND EXPENDITURE BY PROJECT

Project Name	Project Leader	Man Year	DCRT Capital Invested ($ X K) Including Maintenance	Central Facility Charges ($ X K)
		FY-76	FY-76	FY-76
Radiation Therapy, NCI	Syed	3 1/2	65	1
Operating & Recovery Room Monitoring, NCI	Syed	1/2	0	0
Intensive Care Unit, NHLI	Syed	3	32	7
Catheterization Laboratory, NHLI	Syed	1	2	4
Heart Valve Failure Study, NHLI	Schultz	1/2	0	1
ECG S-T Segment Analysis, NHLI	Plexico	1/4	0	2
Ambulatory ECG, NHLI	Syed	1/2	14	0
Lung Test Data Base, NHLI	Plexico	1/2	0	2
Eye Movement Monitor, NEI	Plexico	1/4	0	1
Nuclear Medicine, CC	Schultz	1/3	1	0
Microbiology Data Base, CC	Syed	1/2	0	0
Cell Sorters, NCI	Schultz	1 1/2	0	3
Rat Diet Monitor, NCI	Schultz	3/4		0
Hybrid Computer Replacement, NHLI	Plexico	3	17	15
Potentiometric Titration Controller, NHLI	Plexico	1	1	2
Mass Spectrum Search System, NHLI	Syed	1/2	0	0
Shared Laboratory System, NIAMDD	Schultz	1/2	1	0
Crystal Structure Data, NIAMDD	Schultz	3/4		0
Nuclear Magnetic Resonance, NIAMDD	Schultz	1/3	0	0
McPherson 217 Spectrometer, NIAMDD	Schultz	1	1	0
Mass Spectrometer, NIMH	Schultz	2	17	1
NIH Library	Plexico	2	4	8
Medical Telecommunications	Plexico	1	3	4
Special Consultation		2		1
Internal Programs		3	15	8
Supporting Activities		4	75	10

A. Clinical Care, Diagnosis, etc.

Radiation Therapy, NCI

The Radiation Oncology Branch, NCI seeks to use the detailed anatomical and density information obtained from tomographic scanning techniques (in particular an EMI scanner) to improve radiation therapy planning. This will involve selecting of an appropriate therapy planning computer system with three dimensional capability; devising an efficient method of transferring data from an EMI system to the planning system, and developing an interactive multi-intensity display facility to provide the radiologist with several different representations of body scans and a versatile mechanism for entry of important anatomical and tumor contours. The project began in the fall of 1975. CSL surveyed scientists and business firms working in this field. A DEC PDP-11/70 computer and AECL treatment planning software were ordered in FY76.

Operating and Recovery Room Monitoring, NCI

The Surgery Branch, NCI is considering computer support for patient monitoring activities in its postoperative recovery room and in two associated operating rooms, with special emphasis on respiratory monitoring both as an indicator of physiologic change and as an indicator of life support system failure. In FY76 CSL wrote a request for proposals for components of this system with the intention of developing in-house elements of the system not now available commercially. The project was set aside in the end of FY7 due to problems regarding the space to house this system.

Intensive Care Unit, NHLI

The Intensive Care Unit System developed over the last four years for the Surgery Branch, NHLI provides continuous monitoring of ECG, arterial pressure, venous pressure, temperature, blood loss, and urine output signals, simultaneously from four beds. It was designed specifically to be a versatile, easy to use system, responsive to the demands imposed by ever changing research protocols. During FY76 CSL added the capability to do cardiac output analysis, new user assistance programs, and began development on more elaborate preprocessors for ECG and pressure waveforms.

Catheterization Laboratory, NHLI

CSL has worked with the Cardiology Branch, NHLI to examine the value of on-line computer support for the acquisition and processing of data during cardiac catheterization procedures. Although the accuracy, consistency and manageability of computer associated data collection and computation represents a vast improvement over hand calculation techniques, the importance of the computer in an on-line decision-making role remains an enigma with the consequence that the project is currently being held in abeyance.

Heart Valve Failure Study, NHLI

CSL and the Surgery Branch, NHLI explored noninvasive techniques for the detection of malfunctioning aortic prosthesis using beat-to-beat correlation techniques. Results of this study did not show any improvement over other techniques and the effort has been terminated. The technique and results are discussed in a paper to be published in the fall of 1976.

ECG S-T Segment Analysis, NHLI

The Cardiology Branch, NHLI is interested in studying the effects of drug therapy (e.g., nitroglycerin) on myocardial infarct patients as measured by changes in the elevation/depression of ECG S-T segments. CSL is developing computer programs to make these measurements rather than the current manual method with the thought that, if successful, a micro computer for making the measurements may be developed, allowing for real-time analysis at the bedside. In FY-76 prototype computer programs were written and found to perform well by comparison to manual methods.

Ambulatory ECG, NHLI

The Cardiology Branch of the NHLI is presently recording the electro-cardiogram for 24-hours from ambulatory patients who have demonstrated mild symptoms of coronary artery disease. From this long patient tape, the number of premature ventricular contractions (PVC), the time interval between each PVC and the previous heart beat, and the lowest heart rate are to be determined and utilized in an attempt to identify a high risk group that could be helped with surgical intervention. Discovery of a vendor that would provide the necessary tape processing at a reasonable cost avoided the necessity of CSL effort to design a system.

Lung Test Data Base, NHLI

The Pulmonary Branch, NHLI utilizes automated pulmonary function screen-ing apparatus for its own research tasks and as a pulmonary function service laboratory for NIH. A data base management scheme for the storage and retrieval of test results, both by patient and across patient populations, is necessary. This work, jointly undertaken by CSL and DMB, will entail the transmission of (test results) data already in the laboratory computer via telephone line from the Pulmonary Branch computer to the DCRT IBM 370 central facility, and should be completed late in 1976.

Eye Movement Monitor, NEI

A minicomputer system, selected and procured under CSL guidance, is used by the Clinical Branch, NEI in the study of normal and pathophysiological mechanisms for the control and production of eye movements. The system is based on a similar configuration at UCLA and has been installed and in use for over a year. A new investigator expects to use the system for other research activities and will meet with us in the near future to outline what is required in the way of new instrumentation or new programming support.

Nuclear Medicine, CC

During the past year, CSL has participated with the Nuclear Medicine Branch, CC and LAS, DCRT in the development of the ECG gated heart imaging studies. An improved ECG trigger was designed and fabricated in addition to recabling the entire camera/computer connection, including a switch that allows the selection of input for each computer.

Microbiology Data Base, CC

This project is designed to incorporate Gram Negative Rod data and antibiotic-sensitivity data, available on the Clinical Pathology Computer System, into a data base management system. Equipped with a sophisticated query capability the system facilitates organism identification, the exploration of resistance patterns to antibiotics and detection of the existence and source of hospital infections. In FY-76 we ran the queries and modified the system to meet new research demands. Furthermore, the system was modified to accommodate data from the Honeywell Clinical Pathology Laboratory Computer System, whereas the original system design was to accommodate data from the predecessor system. This project has now been transferred to DMB.

B.   Laboratory Instrumentation

Cell Sorters, NCI

Recent instruments, one developed by Stanford University and Becton-Dickenson and one developed by Los Alamos Scientific Laboratory (LASL) provides for the analysis and separation of viable stained cells in a fluid stream. Analysis is by means of light scatter, coulter volume and fluorescence. NIH, NCI has purchased both of these systems. CSL has added data storage, analysis, and display capabilities to the Fluorescence Activated Cell Separator (FACS) the name of the Stanford System by the addition of a GT44 (PDP-11/40) computer. Currently, an interface to the LASL separator is being designed and fabricated which will allow the GT44 to acquire data from either separator.

Rat Diet Monitor, NCI

CSL replaced an unsatisfactory data logging system used by the Laboratory of Physiology, NCI to monitor the eating behavior of rats that are infected with cancer tumors. The new system included a programmable calculator (WANG 2200) that can, under program control, examine the data on-line while it was being recorded on a cassette. The logging cassette was designed to operate independently of the calculator, thereby, freeing it to perform whatever processing function that is currently desired, including processing previously recorded data read on playback from another compatible tape cassette that was designed into the system.

Hybrid Computer Replacement, NHLI

In late 1974, NIH management determined that some of the space occupied by DCRT's nine year old Hybrid Computer System on the eleventh floor of Building 10 would have to be relinquished in favor of other research programs. CSL developed a PDP-11 System for NHLI, the major hybrid user that occupies only forty percent of the space of the original system. The most critical

phases of this work are now complete, with the result that the Hybrid Computer was removed during May of 1976; additional refinement of the new system will continue for the next several months.

Potentiometric Titration Controller, NHLI

This effort for the Laboratory of Biochemistry, NHLI involves the application of a microcomputer to a new method of controlling potentiometric titration of a solution containing cytochromes. The method involves dynamic introduction of electrical current into the solution while monitoring its potential, optical density and wavelength. Data is directly transmitted to PDP-10 for analysis and transmitted back for display in the Laboratory. System hardware development, including its interface to laboratory instrumentation, is complete; work is continuing on the refinement of algorithms for experimental control.

Mass Spectrum Search System, NHLI

This is a project with the Laboratory of Chemistry, NHLI to relocate some of the Mass Spectrum Search System file creation tasks from the DECsystem 10 to the IBM 370 computer. The effort is directed toward reducing the number of lengthy I/O operations on the DECsystem 10 and improving the reliability of the mass spectrum file creation.

Shared Laboratory System, NIAMDD

CSL continues to support the Laboratory of Molecular Biology and the Laboratory of Chemical Physics, NIAMDD in Building 2 who share a H516 computer that collects data from eight diverse instruments, including two that individually incorporate small computers.

Our efforts, this past year, have concentrated on: identifying and correcting hardware and software problems associated with installation of the Electron Paramagnetic Resonance Spectrometer (EPR) H516 link; performing routine maintenance and engaging in discussion with NIAMDD that will result in a proposal for replacing the H516.

Distributed Microcomputer Prototype, NIAMDD

CSL is developing a local microcomputer system for the Cary 118 Spectrophotometer, one of the heavily used instruments connected to the H516 in Building 2. Our goals for this project are to provide backup for the existing H516 system for this instrument, but the project has a much broader goal which is to prototype a microcomputer system using standard communication protocols and explore the potential for distributed system that does not place real-time data acquisition demands on a time-shared central computer. A system with this architecture could be used to replace the existing Building 2 system. CSL is purchasing a microcomputer system with floppy disks to develop the initial prototype.

Crystal Structure Data, NIAMDD

The Laboratory of Molecular Biology asked the CSL to study and recommend, if appropriate, alternate processing for the large volume of data produced in crystal structure determination. The approach taken was to run representative programs on both the NIH, DCRT IBM 370 and a PDP-11/70, one of the largest midicomputers. Although run times were longer on the 11/70, the 11/70 was purchased with a resulting reduction in total data processing cost.

Nuclear Magnetic Resonance, NIAMDD

CSL has completed the development of a computer system to collect, process and display data from a NMR Spectrometer. In addition, CSL helped purchase a commercial NMR system that became available after CSL development was well underway. The commercial system was significantly smaller and offered convenience and display features that were not present in the CSL system. Rapid scan and new techniques will be the principal uses for the CSL system (built around a Raytheon 704 computer) because the commercial system does not offer any of the software needed for programming new features.

McPherson 217 Spectrometer, NIAMDD

An on-line system for the subtraction of background noise and the production of approximately constant signal/noise ratio has been developed for use by the Laboratory of Chemical Physics with the McPherson 217, a high resolution single beam spectrophotometer. In FY-76 this system was completed and documented.

Mass Spectrometer, NIMH

The Laboratory of Clinical Science, NIMH requested the CSL to develop a Selective Ion Recording System (SIRS) utilizing the LKB90000 gas Chromatograph and Mass Spectrometer and a PDP-11/10 computer which NIMH already owned. A fixed accelerating potential in the LKB will be replaced by a high precision power supply whose output will be under computer control. This potential will focus the instrument and select the ions to be monitored. Data will be acquired and displayed by the computer for each ion selected.

CSL is currently waiting for delivery of the major interfacing components and concurrently proceeding with software development.

C. Biomedical Communications

NIH Library

CSL, in conjunction with the Data Management Branch, DCRT has undertaken the development of a computer based circulation control system for the NIH Library. Based on a PDP-11/40 located in the Library and a communications link to the DCRT IBM-370. The system is based upon machine readable labels affixed to library materials and machine readable patron identification cards. The majority of the computer programming for this system was done in FY-76. Initial system implementation is planned for late summer 1976.

D. Research and Development Projects

Medical Telecommunications

CSL has long had an interest in the development of technology by which computerized medical information can be made available using only a touchtone telephone as a computer terminal. To this end, a microprocessor controlled voice synthesis system which converts computer coded text to spoken English has been developed in FY-75 and FY-76. A completed prototype of this system will be available by the fall of 1976.

III. Publications and Presentations

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Summary of Branch Activities   1.   DCRT

2.   DATA MANAGEMENT BRANCH   3.   <u>J. Emmett Ward</u>
                                          Branch Chief

I.   SUMMARY

Mission and Function

The Data Management Branch (DMB) provides advice and
assistance to research investigators, program officials and
administrators throughout NIH in planning for and obtaining
computer data processing services. In this role the branch
is a central NIH resource for computer systems analysis,
design and programming.

Scope of Activities

DMB staff design and create computer-based data management
systems for specific users and train those users. They also
teach courses about some data management and programming
tools, provide advice on data management techniques to NIH
programmers and serve as consultants on computer based
systems proposed by other NIH groups for implementation by
contractors. Finally, DMB creates and maintains general
purpose, user-oriented programming tools to speed building
and improve operation of specific applications systems.

Design Philosophy

Many computer applications are straightforward. Others
involve an extended period of exploration to define the
users needs, the appropriate information processing
techniques and the computer methods best suited to the
users' circumstances. Clients pay for DMB work under the
NIH service and supply fund as well as for running the
completed systems in the NIH Computer Center. Therefore,
the DMB approach to projects can best be described as
conservative but progressive using, when possible, existing
programming tools to minimize development time and costs and
to maximize system reliability and ease of maintenance.

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The branch develops most systems for operation by the requesting organization. This places control of the completed computer application in the hands of the user, assures each user operational independence from DMB and frees the branch to work on new projects.

1976 Highlights

In FY1976 DMB again worked on more than one hundred projects involving virtually every Bureau, Institute and Division of the NIH. About 30% were projects for applications in-patient care, clinical research, or epidemiology; over 20% for laboratory research areas; almost 40% for program direction, management and administration; approximately 5% for biomedical communications and 5% for development of data processing and analytic tools. About half of the projects each required less than 80 hours of DMB work and another quarter less than 600 hours. The project list in Section II gives a view of the breadth of the DMB work. The following items highlight a few areas of particular interest:

The Clinical Information Utility represents the largest single DMB effort, approximately 3 man-years. It is a joint project between the DMB Clinical Support Section and the Office of Clinical and Management Systems in the NIH Clinical Center to develop a powerful retrieval capability for NIH clinical scientists.

The project began about three years ago with the vast files of data generated by the clinical laboratories in the Clinical Center, about 1.2 million chemical, hematology and microbiological tests per year. Because of this volume the NIH Clinical Laboratories pioneered the use of computers in the 1960s to automate laboratory tests and to record and report daily results. Storing years of data was a task beyond a computer system designed to support laboratory operations. The CIU system receives data from the clinical lab computer system, archives it in the NIH Computer Center and retrieves specific subsets on request.

The initial phase of the project involved many tasks ranging from reconciliation of incompatible file formats and developing a link to the Clinical Center discharge diagnosis file to working out agreements among NIH Clinical Directors and their staffs for accessing the data with privacy protections. After the initial version of the system proved useful, DMB set about to make it perform better and cost less and to keep abreast of changes in the Clinical Laboratories in the NIH Computer Center and in the needs of clinical scientists.

In FY76 work on a new file structure and programs reduced the cost of storing data in the CIU files by about 20%. Work in previous years cut the cost of retrieving data; it is possible to get all data per patient for about eight cents. DilB created an interactive "Retrieval Assistance Program" that permits complete query formulation and job management for CIU retrievals to be done at a remote terminal.

During FY76 Clinical Laboratories installed a new computer system which captures more data per test and now captures bone marrow and microbiology test results. In the coming year surgical pathology data will be made available by the Laboratory of Pathology, NCI with diagnosis encoded in the SNOP (Standard Nomenclature of Pathology) format.

The Retrospective Cardiac Valve Replacement Study project for the Surgery Branch, NHLI, highlights the utility of existing computer based systems and tools. The current project was preceded by several preliminary efforts beginning in 1970, involving a number of NHLI and DMB staff. The decision in FY1975 to develop a comprehensive system to handle data on all open heart operation patients required a redefinition of the system requirements. A master list of candidate patients was generated from the automated Discharge Diagnosis File, searching in specific diagnosis codes, and combined with data extracted from the Clinical Center admissions files.

DMB programming tools ("The generators," described below) aided greatly in converting old computer file record formats and editing the data on more than a dozen record types defined for the new files. The relevant data for all heart valve patients was entered and checked. The system was modified to comply with the new Privacy Act requirements implemented in 1976.

A dual approach was taken to anlysis of the data and generation of reports. The Statistical Analysis System maintained by the DCRT Laboratory of Statistical and Mathematical Methodology provides reliable and flexible sets of tools for extensive analyses. In addition, DMB is writing a program to provide an on-line retrieval and report generating capability for the NHLI surgical staff to interact directly with the data base.

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The Carcinogenesis Bioassay Data System, another long term project, received recognition as public interest grew in carcinogens and other toxic substances in the environment. It was cited in a March 1976 Technical Background Information release about the NCI Kepone studies.

The system serves a managerial as well as a scientific function. The NCI Office of the Associate Director for Carcinogenesis has a scientific program with dozens of contractors performing thousands of tests of compounds on hundreds of thousands of animals.

DMB work on the system began in 1969. The first tasks (Phase I) were creation of programs for data acquisition, editing, input, correction and update, so that NCI would have clean, timely data files and reports on the status of those files. These programs now run reliably in the hands of the NCI data management subcontractors.

Phase II, the programming of specialized reporting and analytic capabilities, has been underway for a year and a half. The approach has centered on a conversational, interactive system that allows NCI staff and others to create and submit requests for reports and analyses from their office terminals. These requests then invoke processing of subsets of the larger data files and are run as batch jobs in the DCRT Computer Center. Phase II will also involve some improvements in the analytic programs themselves.

The Mutagenesis Testing System recently undertaken with the National Institute of Environmental Health Sciences carries bioassay data processing a step further to place computer terminals in the laboratories for direct use by technicians. Design specifications call for an on-line interactive conversational, system capable of supporting several terminals simultaneously to provide data collection under defined protocols. There will also be storage, retrieval and analytic functions. This pilot project will test the thesis that such a system can provide better data collection and monitoring of a coordinated bioassay program at several sites.

The Anti-tumor Preselection System is another beginning
project. It also deals with bioassay data, but will explore
methods for examining existing data on some 10,000 compounds
to assign priorities for further testing in the NCI
anti-tumor screening systems. The NCI Division of Cancer
Treatment has one file of chemical structures of these
compounds with some 30 structural keys assigned to each
compound, and another file designating the activity or
inactivity of each compound in three preliminary assays.
The challenge for DMS will be to develop a system of
programs that can handle the rather large files efficiently
and also be sufficiently flexible to permit trial of a
number of different selection strategies.

The Omnitab II Conversion, a collaborative project with NEI
Office of Biometry and Epidemiology for the benefit of all
NIH, is typical of a class of DMS technical assistance that
often goes unnoted.

The NEI office wanted Omnitab II, a general purpose
"statistical package" created by the National Bureau of
Standards (NBS). They ordered it through the National
Technical Information Service and received a magnetic tape
of the basic programs, a box of punched cards containing the
current program changes and updates, and a copy of the user
and systems programmer manual. The DMS task was to make it
work at NIH.

The system consists of 177 subprograms which are called into
computer core memory in batches ("overlays") as needed.
Although the system was written in "standard" ANSI FORTRAN
changes had to be made for the difference between the NBS
Univac equipment and the NIH IBM machines. To track down
changes and errata not documented in the NTIS manuals, the
DMS programmer leading the project consulted with
programmers who had put the system on computers for the
Federal Highway Administration and also directly with staff
at the NBS. Problems involving the operating system of the
NIH IBM system were worked out through the programmer
assistance (PAL) unit of the DCRT Computer Center Branch.
The DMS staff time was paid for by DCRT's own funds since
this system has potential for many users at NIH.

When the system became operational, the NEI office took over
functional testing to validate the programs and act as
liaison with NIH users. DMS will provide further technical
support if it is needed.

The Unified Generators project is the latest in a continuing series starting in FY1970, which has provided the tools DMB uses in creating systems for its clients. Programs were built to create programs, to establish new data files, to update and reformat existing files, to edit data (that is, check it for conformity to certain criteria) and to create the indices that cut time and cost of retrieval from some files. Each project was done to be compatible with previous projects, but each was for practical purposes a separate system.

The present project unifies these systems and provides a single programming language for routine operations on data files and allows a single definition of editing criteria for a user so that each program generated for a specific use can validate data in the files it reads. These validations can include checks for relationships between items in multiple files.

RMAG is the abbreviated name for both a computer program and a long term project. As the full title (Recursive Macro Actuated Generator) implies, it is used to generate other computer programs and was used in creating the Unified Generators (discussed above) among other projects.

The project began in 1970, when the creator of RMAG joined the DMB. The original RMAG was implemented as a compiler, i.e., a program that functioned in the main batch jobstream of the NIH Computer Center, reading programs written in RMAG language and generating specific programs for users. Over the next few years several very powerful additional arithmetic and logical features were built into it, but its mode of access and use as a compiler remained the same.

In FY76 three new packages were created that make these features, including the macro processing capability of RMAG itself, available as subroutines that can be called by programs written in other languages when those programs are executed on the Computer Center's IBM 370 system. The subroutines were then used to rewrite and improve another part of the RMAG project, a structured assembly language compiler.

The Privacy Act of 1974 affected the way DMB handles projects involving personal data as defined under that public law. The major impact, however, was on handling documents and not on computer programming techniques, since DMB has been sensitive to the need for privacy in the many systems it has developed in recent years.

Future Plans

In FY77 and the foreseeable future, DMB will pursue the same direction that has proven successful over the last few years. There is still a clear need for a central NIH resource for advice, consultation, systems analysis, design and programming on data management applications of computers. The DMB staff has accumulated a wealth of experience in developing NIH data management applications on the NIH Computer Center systems. It has a reputation for reliable, effective work. It has a powerful set of tools to generate new applications and works with experts in other DCRT laboratories when more complex statistical/mathematical analyses and/or engineering skills are required to satisfy a specific need.

DMB projects will continue to arise from the data processing needs of NIH, a remarkable mix in size and substance. The best solution/system for a given problem/project will, of course, depend on the technology available at the time it is undertaken. The prospect of "intelligent" terminals, as well as more powerful software, mean only that more options will be available, not that a given user will get a more complicated or expensive solution/system.

Nevertheless, given new technical capabilities, some data processing needs at NIH will undoubtedly lead to more ambitious projects. Experience shows that large complex projects, involving many users, may flounder for organizational and sociological reasons, as often as technical reasons. Fortunately special attention to planning, training the users, and care in implementation of the system can avoid many of the difficulties. The fact is, however, that the DMB is usually in a technical advisory position when it comes to the overall management of system planning and implementation. Three examples may help to illustrate the kinds of areas for potential concern.

"IMS", the IBM software package for data base management, is now available on the NIH Computer Center. It is being currently used by outside contractors to implement the NIH Materiel Management System and at least one other system in the CC. If IMS handles these projects successfully, there may be interest in its use arising from other parts of NIH. To date the DMB role has been limited to assistance in testing the Materiel Management System.

The Clinical Center is installing the Technicon Medical Information System. This proprietary system will receive and transmit medical orders and reports of test results and some treatment actions in support of medical care. There is likely to be interest among many Institutes in storing and analyzing this information for clinical research or managerial purposes. In the past the DCR involvement has been limited to handling clinical laboratory results in the Clinical Information Utility project. Clinical Trials are an area of continuing if not increasing interest in a number of Institutes. Problems, such as verifying data before input to a computer file and validating analyses of the data are not unique to clinical trials. But when a clinical trial represents a new cooperative project among people or groups who have not done one before, planning for data preparation and analysis should receive as much attention as other aspects of the project.

The resources available in the DCR can provide valuable assistance in assuring the accuracy of any clinical trial effort. The DCR, therefore, expects to be involved in planning the clinical trial and, when appropriate, in developing the software to support it.

II. PROJECT LIST

The list below does not include a number of small new projects and modest revisions and additions to existing systems. These become literally too numerous to mention in an annual report although each is clearly important to the client and requires careful work by the DMP staff.

A. Clinical Research, Patient Care and Epidemiology

1. The Clinical Information Utility

In collaboration with the NIH Clinical Center, Office of Clinical and Management Systems, the DMP Clinical Support Section has entered the second phase of developing and implementing the Clinical Information Utility to provide a powerful retrospective retrieval capability for Clinical Center Chemical Laboratory data. This phase has two primary goals: (1) to increase clinical information coverage, (2) to reduce data management cost.

The newly installed clinical laboratory system has provided more data elements per test and two new data bases: bone marrow and microbiology. Surgical Pathology data will be made available this year with the final diagnoses in SNOP encoded form.

In the first iteration of the CIU System, the cost to maintain and retrieve laboratory results was reduced considerably. Specifically, it was possible to get all clinical laboratory data per patient set for approximately eight cents, but the maintenance cost was far too high. A new file structure has been developed for inverted and data retrieval files during the past year. This has already reduced the cost of building and updating the files by 15 to 25%.

2. Blood Chemistry Study

The Laboratory of Applied Studies, DCPT, has ongoing studies of blood chemistry tests in selected groups of patients and normal subjects, designed to define systematic causes of test results and possible time trends for individuals. DHB staff developed programs to manage the data and perform single, multivariate and time trend analyses. This year's work covered four specific areas, (1) special group study of 18 patients, with 12 weekly samples of 12 chemical constituents; (2) Patient Chemistry Study of 12 chemistry constituents from a group of patients who donated blood samples over a 4-8 week period. This procedure repeats 3-4 times for each patent over a 1-2 year period; (3) Serum pool evaluation of 29 dental student blood samples; (4) Evaluation of 10 chemistry tests on 37 British patients.

3. Evaluation of CC Heart Data

The Endocrinology Branch, NHLI has been the primary user of the system thus far. Statistical analyses programs analyze chemistry data, evaluate demographic information associated with the chemistry data and provide time trend chemistry information.

4. Cardiac Valve Replacement Study
Data Processing System

In support of the Clinical Surgery Branch, NHLI, the DHB developed this system for analysis of the morbidity and mortality of patients who underwent heart valve replacement surgery and to evaluate the various procedures and valves. This year the data base format was completely revised and information on congerital heart valve patients is being added. Two phases of data analysis are in progress: (1) the individual patient's profile following surgery. This analysis includes possible occurrence of embolism, re-operations, anti-coagulant therapy, and changes in patient functional class (quality of life), (2) in-depth evaluation of valve type information. Effort is underway to evaluate embolism, pre-op functional class, valve type, sex, and age to determine the length of patient survival and the post operative quality of life.

5. Type II Intervention Study Computerized Data Processing System

This system was developed in FY71 by the DMB to provide data processing support for an intervention trial being conducted by the Lipid Metabolism Branch of the NHLI. The intervention trial's primary goal is to attempt to determine if the reduction of plasma concentration of low density lipoprotein in patients with Type II hyperlipoproteinemia will cause a regression or decrease the progression of premature coronary disease. This year about 50 additional variables were added to the statistical programs. Both the study and DMB support are ongoing.

6. MAO-Inhibitors

Consultation was provided to the Adult Psychiatry Branch, NIMH, in developing computer formats and coding structures needed to put demographic, behavioral, and chemistry data for a small file of schizophrenic patients into computer processible form for input to statistical packages.

7. Psychogenesis Data Management and Analysis System

A group of programmers from three sections in DMB studied the need for a data management and analysis system which could be used with ease and little computer experience by researchers in the Adult Psychiatry Branch, NIMH.

Because of the cost of implementing and supporting such a system, it was recommended that NIMH use software packages already available within DCRT (Inquiry and Reporting System, Statistical Analysis System) to access and maintain their Wylbur created data files. Assistance in learning and using these systems was provided. When the Technicon System is available for data collection, DMB will review its capabilities and assist the Adult Psychiatry Branch in adapting to it.

8. Cooke Island Filaria Study Data Processing and Analysis System

This system of computer programs was developed this year by DMB to aid the Laboratory of Parasitic Diseases, NIAID in the evaluation and analysis of data obtained during a three month field study of subjects in the Cooke Islands.

9. Kidney Transplant Histocompatibility Study

This system was developed for the Transplantation and
Immunology Branch, JAMDD. Kidney transplant data
pertaining to both Donor and the Recipient from
participating hospitals is submitted to NIH for the study.
Seven different master files are created from multiple
information forms submitted by the 42 hospitals in this
study . DMS's Transactgen is being used to generate seven
single-record type files from the seven multi-record files.
These files will then be the input for seven update programs
which are being generated using the DMS Updategen package.

10. JAMDD Study of the "Incidence and Prevalence Of Kidney and Urinary Tract Diseases"

Data for this study was received from the Air Force, and
Navy for the period January 1971 thru December 1973. All
data was converted by DMS to a standard format and tables
were run for each service in total and by year showing
diagnoses codes by age group, sex and race. At present due
to wide differences in results of Army data as compared to
Air Force and Navy data, the Associate Director for Kidney,
Urologic and Blood Diseases Program, JAMDD has requested
that the Army recheck their data.

11. Basement Membrane Study

The intent of this system is to support the JAMDD Field
Studies Section in evaluating the Siperstein basement
membrane method of predicting the onset of, as well as
diagnosing the existence of overt diabetes. Current plans
are to apply the Siperstein method to a known Pima Indian
population and a Caucasian normal group. Dr. Siperstein and
Dr. Williamson are to provide basement membrane measurements
for this population and their criteria for evaluating the
measurements for (1) Prediabetic, (2) Normal, (3) Diabetic,
Recent-Onset, (4) Diabetic, Long term without complications,
(5) Diabetic, Long term with complications. Initial
programs will simply match results to known information to
test the credibility of the Siperstein method within defined
confidence limits. This effort will also include an attempt
to both identify and eliminate sources of variation.

12. Lupus Study (NIAID)

This study involves a predefined and specifically described comparison of the effects of three drug programs on the diffuse glomerulonephritis of Systemic Lupus Erythematosus (SLE). Thirty-eight patients were initially randomized into one of the three predefined protocols as follows: 1) prednisone alone, or 2) cyclophosphamide and prednisone; or 3) azaphioprine and prednisone. In FY74, the DMB developed a system for correlating drug administrations and laboratory results within a clinical protocol. These programs have been reactivited and are currently being enhanced for future protocol monitoring.

13. Cancer Survival System

The Survival System was originally developed for the NCI to support the End Results in Cancer studies involving survival probabilities of patients observed throughout the U.S. with relation to treatments, age, sex, stages of disease, etc. A new version of the system was made available during FY76. A number of changes were made to support changes in formats and data code values. In collaboration with the Cancer End Results Section, the Users' manual was completely overhauled.

14. EVIF Medical Records Information System

This system has been redesigned by DMB for the Emergency Virus Isolation Facility, Viral Oncology Branch, NCI. The system provides storage and retrieval of medical records information on employees of the facility. It has been expanded to accommodate serum sample management data for employees of contractors working with the facility and modified to permit on-line entry of data.

15. Cutting Oil Study

This project supports the efforts of the National Institute of Occupational Safety and Health in a study relating job type to mortality and morbidity of cutting oil workers. During FY76 DMB completed one set of survival or life table analyses, and progress was made on a second set.

16. Computerized Daily Work Load Data Storage and Reporting System

This system is being developed by DMS for the NIH Employee Health Service to collect information on employees seen at the various EHS units in order to improve data management efficiency and to increase the reporting capabilities of that office. Reporting includes monthly reports of workload, annual reports on types of treatment illness and injury rate reports, workman's compensation information, scheduling of physical examinations, scheduling of repeat testing and scheduling of special tests.

C. Laboratory Research

1. Carcinogenesis Bioassay Data System

This computerized data processing system makes it possible for the office of the Associate Scientific Director for Carcinogenesis, NCI to control the data acquisition, input, purfication, reporting and analysis of animal experiment data and the identification of the many agents used in carcinogenesis experiments. A conversational analysis system builds parameter cards and JCL for batch runs and contains a statistical description program for counting animals with specific pathologies. A program generating regular survival curves, Kaplan-Meier curves, and the Breslow statistic is currently being incor porated into the terminal system.

2. Preselection Methods for Antitumor Chemicals and Drugs

DMS is collaborating with Division of Cancer Treatment, NCI. NCI has a file of structure keys, and a file designating activity or inactivity of 19,000 chemical structures for each of three tumor test systems. Methods are being explored to use activity information along with key frequency information to assign priority of compound screening in various test systems.

3. Carcinogenesis Activity Survey System

DMB established a data file for the Carcinogenesis Branch, NCI that can be machine read and searched for all of the previously published volumes of the PHS-149 series: "Survey of Compounds Which Have Been Tested for Carcinogenic Activity." Programs to format, edit and update the data have been written along with the necessary query capability to retrieve from the file. During the coming year more data will be added to the file as new volumes are published. The user has also requested a "string searching" capability.

4. Evaluation of Bio-Assays

In collaboration with the Laboratory of Biochemical Genetics, NHLI, DMB has implemented a set of programs to compute the best fit passing thru the origin (with zero intercept), and to use the computed slope to predict such potency parameters as dilution factor, milligrams per reaction mixture, micrograms per plate; with varying concentrations and samples.

5. Scintillation Counter

DMB supports programs provided to the Laboratory of Chemistry, NIAMDD for performing analytic calculations on scintillation counter data and plotting the manipulated data. During the year new input formats were added to allow use of a new scintillation counter purchased by the Lab. In the future we will continue to add new input formats whenever new instruments are purchased, and add more efficiency correction equations as new types of experiments are undertaken.

6. Multiphasic Zone Electrophoresis Programs

This set of programs, for the Reproduction Research Branch, NICHD, models the application of Polyacrylamide gel eletrophoresis (PAGE) to the entire PH range and generates buffer systems giving a complete physical description or 'recipe' for each system. The output from these programs (2000 theoretically generated recipes for gel electrophoresis systems) is being distributed on tape to universities and laboratories by NTIS. As part of our continued support of this project, microfiche copies from the output tapes were generated for distribution by NICHD and eventually, NTIS. In addition, a program was written which allows automatically retrieved systems to be summarized and put into a 'recipe form' for use in the lab.

7. NIEHS Mutagenesis Testing System

This system will provide programs for the Environmental Biometry Branch of the National Institute of Environmental Health Sciences to monitor the protocol for mutagenesis testing. Design specifications call for multi-terminal, on-line, conversational program package to interface with laboratory technicians and provide controlled data collection, data storage, and data analysis. This is a pilot project and will be tested under live conditions as part of a current mutagenesis research contract.

8. Transport Studies in Ischemia

A program was written for Laboratory of Neuropathology and Neuroanatomical Sciences, NINCDS to perform calculations needed for analysis of double isotope data from a scintillation counter in support of ischemia studies in rabbits. Instructions in using the IBM/360 systems via Wylbur to enter data and to run the computer programs was provided.

9. Brain Catecholamines

The Laboratory of Clinical Sciences, NIMH is measuring brain catecholamines in rats for a variety of purposes: for example, to study the effect of stress on the neurotransmitters of the brain. A program was provided which performs calculations on the scintillation counter output for norepinephrine, dopamine, and protein assays. LSMM provided assistance in the selection and use of statistical packages for producing one-way analysis of variance and t-tests on the results of these calculations.

C. Program Direction, Management
    and Administration

1. System for On-Line Control of Resource
    Allocation and Trend Evaluation (SOCRATES)

This system was developed by DMB for the HANDP. The system
has been improved considerably during the past year. The
new modules are:

ZEUS - This module is used only by the SOCRATES' controller
to register users and to control access to all information
retrieval modules.

DESCARTE - This module permits the user to select a subset
of information from a data base, and generates a record
definition table for the retrieval modules. It operates in
batch-mode under on-line control and provides the name of
all data elements in each unit record and defines their
locations, lengths, and formats. Because the record
description table drives the retrieval program, changes
affect only the table, not the program.

GAUSS - This is a generalized module designed to select and
display information from data bases maintained by other
components.

APOLLO - RMAG logic subroutines have been added to SOCRATES
for the retrieval modules.

2. Case Reports, 1975

This annual reporting project for Office of Research
Analysis, O.D. summarized DHEW awards to institutions of
higher education, health professional schools, nonprofit
hospitals, nonprofit research institutes and operating
foundations, and R & D centers. New editing and balancing
procedures were implemented for the FY75 data. Only 25
general summary tables were published this year as compared
to 130 in previous years. A query capability was provided
to supplement these reports as needed.

3. Computerized Grants Information System

Designed in FY75, this system was implemented in FY76 by the
DHB for the Program Analysis and Evaluation Branch, Division
of Cancer Grants, NCI. It provides a complete file
maintenance, ad hoc query capability and keyword index
search capability on NCI grants information.

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4.   NICHD Grants System

The Grants and Contracts files were reformatted by DMS for the Office of Planning and Analysis to provide additional codes for scientific classification. A query capability and documentation for using this facility were provided to NICHD personnel, who are running the system.

5.   Index Information Systems

The 1974 and the 1975 NIH Grants Abstracts files were indexed for retrieval purposes, using the DMB Indexing facility for the Research Analysis and Evaluation Branch, DRG. This was only one of several uses of the DMB Indexing Facility, but it is worth mentioning because of its size.

6.   Combined NIH Mailing List System

During FY75, DMS developed this system for the Grant and Contract Guide Distribution Center of DRG. The system creates, maintains and selectively produces labels to be used in the distribution of the Grant Contract Guide and any of its various supplements. The system has four primary objectives, (1) reduce redundancy, (2) simplify the maintenance effort, (3) enable faster service and (4) provide extremely powerful selectivity. The data base currently houses approximately 53,000 individuals' names and is continually being augmented. This year the system was refined to allow DRG to expand and control all facilities without additional programming.

7.   Division of Research Services Support

These systems aid the DRS in maintaining and controlling the following activities: 1) The Glassware Billing System; 2) The Small Animal Billing System; and 3) The Planning System. These systems have been in production since the beginning of the fiscal year but maintenance program modifications required by DRS are being provided as needed.

8.   NIH Personnel Accident Reporting System

The Accident Reporting System was developed, during FY74 by DMS for the NIH Office of Administrative Services, Protection and Safety Management Branch to aid that office in the processing and reporting of NIH employee accidents and related information. This year a query facility was added and a new set of recurring reports is being defined.

9. NIH International Activities and
    Personnel Monitoring System

This system was developed three years ago by the DMB to help
the Fogarty International Center maintain and query a data
base containing information on Foreign Visiting Programs,
Foreign Guest Workers at NIH, and Foreign Visitors at NIH.
This year the file maintenance system was restructured to
run in 'G' class, thereby making it more responsive and a
new summary report was written.

10. "The National Clearinghouse for Capacity
    Building and Human Services
    Integration" Program

The clearinghouse service is being provided by the Aspen
Systems Corp. under a DHEW contract. In support of this
effort, the DMB developed a system of programs to maintain
and control the file of subscribers to the service.

D. Biomedical Communications

1. Selective Dissemination of
    Information (SDI)

A current awareness search for Chemical Biological
Activities (CBAC) is offered to all researchers at NIH and
is run biweekly as tapes are received from Chemical
Abstracts Service in Columbus, Ohio. Retrospective requests
are being referred to the on-line service, TOXLINE,
available at NLM.

Similarly a current awareness search of Biosciences
Information System (BIOSIS) uses tapes received twice
monthly from the Biological Abstracts Service.

The NIH Library has been the primary contact with the NIH
researcher wishing to search this data base; the Library
submits researcher profiles to DMB for Current Awareness
searching, and to NLM for retrospective searching.

Personnel from the NIH Library and from DMB took part in an
all-day seminar presented by Biosciences Information Service
in Philadelphia. DMB represented NIH on a users' panel
consisting of SDI personnel from SUNY, Lockheed, Dept. of
Agriculture and NIH.

2. NIH Central Library Circulation System

DMB developed an IBM-370 interface with the PDP-11 computer being developed by the Computer Systems Laboratory, DCRT, to collect daily library circulation information. Programs which monitor library activity were procured by the NIH library and the DMB staff converted these programs to run on the DCRT IBM-370 system.

3. Gastroenterology Data Base

This is a pilot project for NIAMDD to determine the usefulness of computerizing a data base of journal abstracts from the literature of Gastroenterology. Reformat and print programs were written. The CBAC system was utilized for searching the text.

Searches run on the data base in order to explore the completeness of the file and the utility of the search indicated that automatic searching would not be cost effective at this time. During FY76 DMB continued computer monitoring of contractor tapes containing journal abstracts and ran the DMB Concordance program on the accumulated data for the year to produce a KWIC index for manual searching.

4. Journal of the National Cancer
Institute (JNCI) Computer System

This system was developed by DMB in FY75 for the Division of Cancer Cause and Prevention, NCI to assist the Office of the Editor-In-Chief in logging newly received manuscripts, tracing manuscripts through the various review stations, producing correspondence, etc. This year the update procedure was revised and programs for producing author indexes on microfiche, for designating manuscript assignment status and for handling mailing lists were developed.

5. "Audiovisual Materials in Dental Education"

A system of programs has been written by DMB to produce a publication for the National Medical Audiovisual Center in Atlanta, Ca. These programs create the 1) "Subject-Title Index; and 2) "Descriptions of Audiovisual Materials" which lists, alphabetically by title, the available publications and the audiovisual media associated with them.

E.   Tools for Data Management and Analysis

1.   Unified Generators for Creation, Maintenance, and Retrieval of Data

This CMB project involves development of a special-purpose,
high-level programming language for routine operations on
data files. Programs can now be generated a) to create and
update files using key-oriented transactions, b) to reformat
data files, and c) to index textual data from files (file
inversion). Files are assumed to have, in general, multiple
logical records per subject.   Any generated program can
validate or error-check data in the files it reads, using
conditions   involving   relations   between   fields.
Documentation exists for the completed parts of the system.

2.   Recursive Macro Actuated Generator (RMAG) Project

RMAG is a programming language used for the generation of
source programming languages and DATA/TEXT strings. The
main thrust this year has been to make many of the RMAG
capabilities available as subroutines, callable from any of
the standard programming languages, to provide programmers
with sophisticated user communications capabilities.

Three packages have been written, debugged, documented, and
placed into an available load module library. Coding was
done using RMAGASL, the RMAG21-coded structured-programming
compiler.

> The   logic   subroutines   package   handles
> sentential calculus expressions at   run
> time.   With it comprehensive retrieval
> systems can be programmed and run within a few
> days.

> The arithmetic subroutine package handles
> arithmetic   expressions   at   run   time
> analyzing   and   evaluating   expressions
> containing   some   50   operators,   nested
> parentheses, and deeply embedded replacement
> operators.   The   operator   set   permits
> integer   arithmetic,   logical,   relational,
> truth-functional,   and   machine-language
> bit-manipulating functions.

> RMAG22 available as a callable subroutine
> at   run time--enabling easy sophisticated
> macro specifications.

The above three sets of subroutines were all then employed in rewriting the RMAG structured programming compiler. The new product, known as RMACASH2, is more powerful and much faster than the original.

3. Inquiry and Reporting System (IRS)

IRS is a proprietary package developed by Sigma Data Corporation. During FY75 DMB continued its user support of this system. This includes maintaining the integrity of IRS by testing new IRS releases and notifying users of changes to IRS, keeping informed about DCRT hardware/software changes that may affect the operation of IRS, and providing IRS classes. During the year a new release was installed and preparations were made for the conversion from OS to MVS.

4. OMNITAB II Conversion

OMNITAB II is a user-oriented system for problems involving numerical, statistical, and data analysis. Developed at the National Bureau of Standards, it was installed at DCRT for the Office of Biometry and Epidemiology, National Eye Institute. The system consists of 177 ANSI Fortran subprograms and contains an overlay structure of 14 segments and 9 subsegments. Operation of the system has been turned over to NEI and functional testing of the system is currently in progress. The NEI will act as liaison for NIH users and DMB will provide technical support when required.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities   1.   DCRT

2.   Computer Center Branch   3.   Joseph D. Naughton
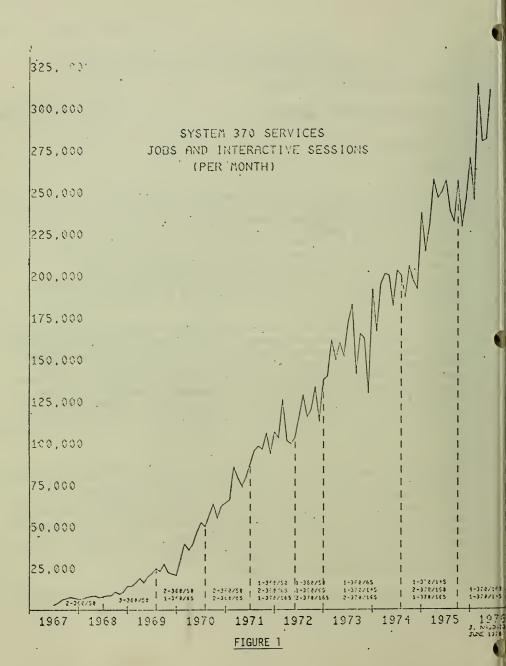   Chief

I.   SUMMARY

Function

The Computer Center Branch was established to provide reliable,
accessible, effective central computational services for the NIH
on a fee-for-service basis under the NIH Revolving Fund.   Its
objective is to incorporate proven advances in computer
technology into a simple, reliable utility for the needs of NIH.
The need to preserve the integrity of data and insure the
integrity of the computing system outweighs all other
considerations.   The challenge is to achieve new improvements
without lowering the quality of service to science and its
management at NIH.

The NIH Computer Center has designed and implemented a powerful,
modern system network of computers and communication facilities.
The nucleus is composed of two large multi-computer subsystems,
each having advantages for certain kinds of computing.   The
communications facilities link these two subsystems and connect
them by telephone lines to over a thousand remotely located
terminals of various types.   The computing and communications
equipment are controlled and balanced by very complex programs
(systems software) designed and created by the Center or acquired
from other sources and adapted to NIH needs.

Services and facilities of the Center include standard
programming languages (e.g., FORTRAN, COBOL, PL/I, SAIL, Assembly
Language) and a library of utility programs.   For users with
terminals there are also interactive systems (WYLBUR, TSO, DEC
time-sharing), which facilitate creation, submission and output
of jobs and permit direct interactive computing (using FORTRAN,
BASIC, CPS, APL, MLAB and other languages).   The Center also
provides a variety of facilities for output of printed material
or graphics on paper and microfilm as well as two and three
dimensional cathode ray displays.

Finally, the Center provides extensive training, documentation,
information services and trouble shooting assistance for its
users.

SYSTEM 370 SERVICES
JOBS AND INTERACTIVE SESSIONS
(PER MONTH)

FIGURE 1

141.1

Scope of Work

The Computer Center, with a staff of 150 people, operates 24
hours a day, for over 4,000 users, including all NIH Bureaus,
Institutes, Divisons and Offices. During FY76, the workload
handled by the Center grew 25%. (Figure one is a chart of growth
since 1967.) At year's end, the Center was handling over 300,000
jobs and sessions per month. This number includes 7,000
mainstream jobs a day processed by the utility, with 80% of them
completed within one hour. Interactive timesharing sessions via
remote terminals have risen to over 3,600 a day. The ratio of
"jobs" to "sessions" increased during the last year, despite
continued growth in use of the interactive facilities.

Highlights of the Year's Activities

FY76 was an extension of the Computer Center's nine year history
of planned introduction and integration of facilities and
services capabilities in response to the unique needs of the NIH
user community and other new requirements such as The Privacy Act
of 1974. The two major systems were upgraded, communication
facilities were improved, computer programs and graphics
facilities were revised to meet user needs more effectively, and
CCB staff provided extensive user education and assistance.

Upgrading of Systems

. System Upgrade: IBM 370. To meet the challenge of the growing
workload and to keep a fast yet reliable turnaround, a major
hardware upgrade was made to the IBM 370 system. A second IBM
370/168-MP central processor and memory complex was installed
replacing the slower and smaller (memory) IBM 370/165. The
installation, although delayed by GSA's procurement procedures
and construction difficulties, was operational in October and job
completion time returned to the standard set by the Center. A
number of other hardware changes took place which augmented
available on-line storage and increased the rate of data set
transfer among the system components. These also prepared the
way for a staged major conversion to new "virtual memory"
operating system software (OS-MVS), which will permit more
effective use of both new vendor-supplied capabilities and the
Center's own system software and machine configuration.

. System Upgrade: DEC-10. The DEC-10 system underwent a
comparable but more extensive upgrade. Operating system changes
included virtual storage capability and an improved internal
queuing facility for handling multiple users and jobs. The
central processors were upgraded and the central core memory
shared by them was doubled. Equally important was the
replacement of older on-line disk storage units and tape drives

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with a larger number of new models, which provide more compact
storage, faster data transfer, better automatic error detection
and correction and greater compatibility with other Computer
Center systems. A new printer and a new plotter provide more
flexible, better quality output and a new paper tape reader
accepts reels of tape generated by many NIH laboratory
instruments.

Communication Network Improvements

Communication facilities are essential to make the power of
modern computing systems available to the NIH scientific and
administrative staff in the environment where they work. Much of
the work in FY76 was again directed toward making the
capabilities of both the IBM 370 and the DEC-10 systems
accessible through the same terminal devices, as well as
accommodating terminals with a broader range of functions and
increasing the communication speeds. This is the result of
several years of planning and matching hardware from several
sources: computer vendors, communications equipment companies,
the telephone company and its NIH facilities and terminal
manufacturers. It also required planning and writing
communications software.

. Improved Communication Speeds. In recent years the standard
equipment for communication from keyboard terminals over regular
voice grade telephone lines limited transmission rates to 10 to
30 characters per second. This is adequate for typing in
commands, data and other information on a terminal but this speed
proved to be a greater and greater handicap in displaying
information coming back from the computer.

Taking advantage of newer equipment, in FY76 the Computer Center
upgraded its communication speeds to 120 characters per second
(120 cps). This makes a 4 to 12-fold time saving possible in
portions of the terminal dialog with a computer. This saves time
and hence communication charges for users, and shorter terminal
sessions free up lines at the computer end for other users.

The center also increased communication speeds for Remote Job
Entry (RJE) terminals which permit work to be submitted and
printed results to be returned directly to the laboratory or
office. Again the major time savings will probably come in
output from the computer, since RJE terminals are installed
primarily where an on-site printer capability is needed. This
year facilities were added to the DEC-10 system to communicate
with the 370 system.

. The NIH5200 Terminal. An essential part of the communications
planning over the last few years concerned getting a new terminal

that fits properly into the overall computing system at NIH. The Center's specifications went out for competitive bidding, and in FY76, the first 100 units of the NIH5200 terminal were installed. It is a cathode ray tube (CRT) terminal with a keyboard that communicates at the new higher speed (120 cps) with both the IBM 370 and the DEC-10 systems. A small printer (120 cps) is available for users who need "hard copy" output.

. Improved MILTEN. No terminal communicates with a computer unless there is a program at the other end of the line to handle the communications. MILTEN is such a program that runs on the IBM 370 system, and handles a variety of terminals. During the year MILTEN was revised in several parts to handle increased communication speeds and to take advantage of the capabilities of the NIH5200 terminals.

Services and Facilities

Computer Center users are primarily interested in what they can do with a computer. Systems upgrades and faster communications are important for responsiveness and reliability but the payoff for many users comes in new kinds of services and facilities or better versions of old ones.

. Improved Graphics. The Center's planning for improved graphic output resulted in the integration of its graphics facilities under a single software facility, the Integrated Plotting Package (IPP). The same commands and subroutines may now be used for any of the devices available to the 370 system users: graphic scopes, mechanical plotting or microfilm output. A new mechanical plotter (Calcomp 925/1076) is faster, more accurate and capable of multicolor line drawings. IPP was augmented to drive Tektronix 4010 graphic terminals which previously could use only the DEC-10 system.

Graphics on the DEC-10 system had previously been integrated under the OMNIGRAPH software, which services 8 different kinds of display terminals and 3 plotting devices. On-line plotting was improved this year by support for a new model ZETA plotter that can use the 120 cps communication facility. The DEC-10 system can also direct output to the new off-line Calcomp plotter for larger drawings, and new facilities were added during the year to allow text or graphic output via the microfiche facilities on the 370 system.

The counterpart of graphic output is input from line drawings for mathematical analysis. This year the Center staff developed and installed a program called DIGIT that permits tracing curves from laboratory equipment with automatic conversion to computer processable information. DIGIT makes use of an existing graphic

display system on the DEC-10 system, which contains a RAND tablet and tracing stylus.

. _Programming Facilities_. For the IBM 370 system the Center obtained and installed a program performance monitor called PROGLOOK. This permits programmers to get timings for specific portions of a running computing job and determine where major time savings might be made by reprogramming. The current interest in structured assembly language programming was supported by installation of an assembly language preprocessor.

DEC-10 users continued to benefit from APL, a language that many programmers find useful, particularly for mathematical programming. A new document processor called PUB was provided. It has a number of particularly powerful capabilities for formatting text with columns, footnotes, paragraphs and tables as well as the usual text justification, page numbering, etc. It also can create indices and tables of contents.

. _User Education and Assistance_. A crucial factor in the effectiveness of any computer center is aid to its users in learning how to use its facilities and overcome problems. For the eighth successive year the Computer Center Branch organized both a fall and spring term of Computer Training Courses and Seminars. These courses covered its entire range of general purpose programming languages and special facilities and programming aids.

Members of other DCRT laboratories and branches taught the use of statistical and mathematical packages (BMD, SAS, SPSS, PSTAT, MLAB, MODELAIDE), query and reporting facilities (IRS), and programming tools (RMAG 21, PDP-11 tools). Seminars taught by DCRT mathematicians and scientists covered such diverse topics as laboratory computers, time series analysis, Macro molecule ligand binding models, pattern recognition, diffusion and biophysical techniques.

The Center's Technical Information Office stocked and distributed some 50,000 copies of thirty technical reference manuals and guides and the Computer Center Users Guide. The Guide was completely rewritten and many of the manuals were revised. A new PL/I Programming Techniques Library and a JCL (job control language) primer were offered, along with a number of programmed instruction courses for Center users who want to learn at their own convenience.

Equally important, the Center helped its users solve and avoid problems. The Technical Information Office used its automated files to make sure that users received new or revised copies of any manuals they had previously received. (The DEC-10 system

alone had 11 new manuals.) The Center published and distributed
six issues of INTERFACE, its technical notes covering new
facilities, procedures, diagnostics and hints as well as
recognized "bugs" and ways to avoid them.

The programming assistance and liaison (PAL) unit recived and
helped with more than 10,000 personal or telephone inquiries and
analyzed some 3,000 written programmer trouble reports (PTRs).

. <u>Coping with Growth</u>. Success over the last nine years in
meeting the NIH needs for computing power has brought the Center
some problems. The amount of work processed has grown more than
50-fold. The increase in computer hardware and the tape and disk
library has been a mere fraction of that magnitude, but was
enough to crowd the machine room space in Building 12 beyond
reasonable limits. During FY76 the Center had to move its
production unit and the user output boxes out into the halls of
Building 12A. To provide adequate on-line disk space for data
storage on the 370 system a temporary machine room was created on
the second floor of Building 12, directly above the main machine
room.

. <u>Privacy</u>. The Privacy Act of 1974 occupied a most important
position in all Computer Center activities this year, as it will
in the future. The Computer Center has developed and is
implementing its security plan to provide proper protection of
personal data and equipment as required by the new law. Access
to the computer areas is now controlled; only authorized
personnel are permitted in the areas and they must be identified
by badge.

<u>Future Plans</u>

Completion of Building 12B in FY77 will eventually allow the
Computer Center to house all of its user-oriented facilities
properly on the first floor of Building 12A. Plans are underway
to provide locked user output boxes, comparable to post office
boxes. This will mean even better separation of the computer
operators from public areas, as required under the Privacy Act.

Conversion of the IBM 370 system to the new MVS (Multiple Virtual
Storage) operating system will be completed. The change will
take place in planned stages, using the unique software "bridge"
designed by the systems team to allow connection between the old
and new systems and insure a smooth transition.

A major step forward for system 370 terminal users will come with
the release of NEW WYLBUR, a completely redesigned version of the
Center's most popular interactive system. This new version will
support more simultaneous users and will provide many new
features to make it more powerful and easier to use.

A new, more powerful graphic capability is planned for the DEC-10 system to replace the existing AGT-30 and DEC-340 terminal. This will provide greater support for scientific users in modeling macro molecules and submolecular structures based on crystallographic and microscopic data.

The communication link between the IBM 370 and DEC-10 systems will be expanded with software facilities to allow both systems to handle data sets for those functions that are best done by each system.

This optimistic projection is clouded by the fact that many key CCB professional staff have become progressively tied down in seemingly interminable technical discussions with the General Services Administration in new hardware procurement matters such as the re-bidding for the NIH5200 terminals. In addition, a great deal of time last year went into diagnosing and documenting major problems encountered in disk packs and magnetic tape that NIH was required by GSA regulations to buy off the Federal Supply Schedule. It is difficult to predict how much staff time will diverted by similar problems in FY77.

PERIOD COVERED
July 1, 1975 - June 30, 1976

TITLE OF PROJECT (80 characters or less)
Atlas of Macromolecular Structure on Microfiche (AMSOM)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.   Richard J. Feldmann, CCB, DCRT, Computer Specialist

Other: R.L. Tate, Ph.D., CSL, DCRT, Senior Staff Fellow

COOPERATING UNITS (if any)
Department of Chemistry, Brookhaven National Laboratory

LAB/BRANCH
Computer Center Branch

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bldg. 12A, Room 3009, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0

SUMMARY OF WORK (200 words or less - underline keywords)

The three-dimensional structures of many biologically important macro-molecules have been determined by X-ray crystallography. The purpose of this project is to bring together all of the atomic coordinate data representing these macromolecules, to reduce all of the data to a con-sistent form and style, and to prepare for publication an atlas of these macromolecules. The information is presented on microfiche in both textual and graphical form. Different structural aspects and sections of the macromolecules can be perceived in stereo on the screen of a microfiche viewer using a box attachment which contains polarizing material and a half-silvered mirror. The atlas will be updated as new structures are made available.

Atlas of Macromolecular Structure on Microfiche

The determination of the atomic structure of biologically important macromole-
cules is being done at various laboratories throughout the world. The struc-
ture determination is done by X-ray crystallography and the result of this
work is a set of atomic coordinates. A data bank has been formed at Brook-
haven National Laboratory for collecting this data. Aside from the presenta-
tion of a few views of these complex molecules in journal articles, there had
been no graphical way of adequately presenting this type of information.
Stereo perception of the spatial relationships in the data is absolutely essen-
tial. This project originated when a link was established between the NIH
DECsystem-10 on which there are programs for displaying and manipulating macro-
molecules and the NIH IBM-370 system which has the ability to generate textual
and graphical microfiche. Test microfiche were used to estimate the interest
and value of this approach to different types of biochemical scientists. The
response of the scientific community was very strong.

The Atlas of Macromolecular Structure on Microfiche (AMSOM) is now in the
final stages of preparation for publication under a contract which was signed
this year. It will consist of 650 microfiche, a stereo viewing box, viewing
glasses and an index volume which contains a bibliography and has pointers to
the structural features in the microfiche. The atlas package is now being
prepared under contract and should be available to the scientific community
in late 1976.

The rate at which structures and structure variational states are being done
is increasingly exponentially. When the project was started only 15 structures
were available, partly as a result of this project there are now about 75 struc-
tures available in a consistent format. Thirty five of these structures were
added to the file in the last year. In addition, a comprehensive bibliography
was generated during this year of all the currently available structures as
well as all the structures still in the process of structure determination.
The AMSOM system should be able to cope with the expected buildup in the num-
ber of structures. As additional structures become available the atlas will
be updated.

In addition, there is the possibility of applying this information dissemin-
ation technique to other scientific data, such as the structure of small
organic molecules.

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

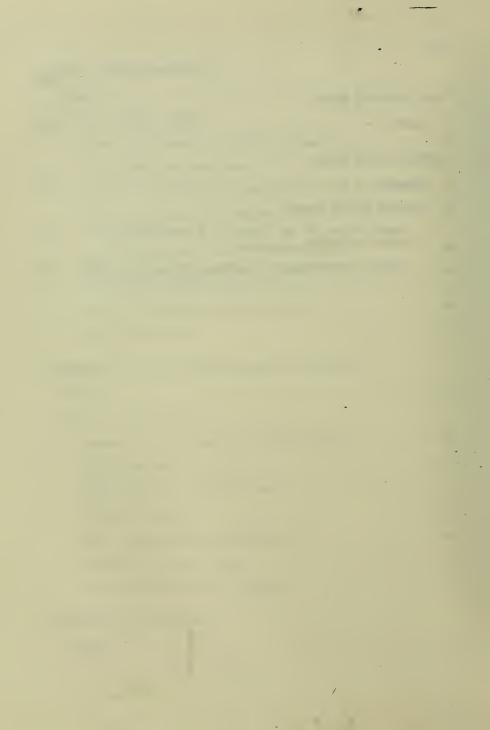Report of Program Activities

July 1, 1976 through September 30, 1977

ANNUAL REPORT

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DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

July 1, 1976 - September 30, 1977

DIRECTOR'S SUMMARY

During FY'77, the NIH made substantial progress in computer research and tech-
nology and in the use of computers in the conduct of biomedical research and
its administration. The role of the Division of Computer Research and Tech-
nology in this satisfying enterprise is set forth in the details of its
annual report. Some highlights are presented in this Summary.

But the next few years may be remembered as both the best of times and the
worst of times for computing at NIH. Therefore this Summary also discusses
some problems in Program Balance and Resource Allocation and three contra-
dictions seen in the larger perspective.

The Magnitude of Computing at NIH

In FY'77 there were over 4000 NIH users of NIH computer systems. This number
includes 2800 registered users of the central DCRT computer system, 1500 of
the Clinical Center Hospital Information System, 230 of the NLM computer-
based systems and well over 100 users of the other fifty smaller computers
around NIH. At least one third of the NIH staff uses computers in some way
and the number is still increasing!

The reasons for this computing endemic lie in the nature of the NIH work. The
primary materials used in the support and conduct of biomedical science are a
great variety of scientific and administrative data and other kinds of infor-
mation. As the preeminent information processing machine, the modern elec-
tronic computer has found application in all NIH activities: clinical research,
patient care, epidemiology, laboratory investigation, management of grants and
contracts, biomedical communications, program direction and a wide variety of
administrative functions.

The Role of DCRT

The Division was established in 1964 to make an emerging computer technology
useful at NIH. DCRT embodies expertise in electronic engineering, computer
science and technology, mathematics and statistics, and a variety of scien-
tific disciplines including physics, chemistry, medicine and linguistics. The
DCRT is a central intellectual and technical resource for all NIH.

Its objectives have been to develop distributed computing capacity throughout
NIH, using large, medium-sized and small computers where each is appropriate,
to make users of its services and facilities as capable and independent as
possible, and to incorporate the expertise and experience of its staff in
good science and sound administration at NIH.

The Division carries on this work in six laboratories and branches:

The Computer Center Branch (CCB) designs, implements and maintains the central NIH computing utility, accessible day and night to thousands of users from hundreds of terminals where they work. During FY'77 this utility logged over a million interactive terminal sessions by its users and more than two million jobs done in its central job stream. The NIH computer center continues to be recognized by many other federal agencies and by experts in the private sector as the most accessible, reliable and comprehensive computer facility in the Federal government.

The Data Management Branch (DMB) and the Laboratory of Statistical and Mathematical Methodology (LSM) make this central computing power useful for the specific tasks of hundreds of NIH scientific and administrative users. LSM and DMB have built and acquired a powerful library of statistical, mathematical and data management software tools to meet NIH needs. They provide consultation and advice to users and develop new programs for them when the existing packages are not appropriate for particular tasks.

The Computer Systems Laboratory (CSL) uses its engineering expertise to design and develop computer systems to handle tasks for which the central NIH computing utility is not the appropriate resource. Many of its products and ideas have been copied and adopted by other organizations. CSL also serves as consultant to other groups at NIH in the procurement of small computers.

The Laboratory of Applied Studies (LAS) and the Physical Sciences Laboratory (PSL) carry on collaborative projects with scientists at NIH and outside NIH. They also serve as consultants on the use of mathematical theory and computing methods in biochemistry, biophysics and clinical medicine.

All six branches and laboratories are involved both in collaborative or service projects and in research and development to generate new techniques and theories. Members of the labs and branches also teach courses in computer technique and give seminars on topics of interest in computer applications.

HIGHLIGHTS OF FY'77 ACTIVITIES

The following highlights offer a broad overview of DCRT work during the year and a sense of the directions it is taking. The DCRT services and facilities that support many NIH activities are covered first, followed by specific projects that illustrate DCRT work in the clinic and laboratory and administrative domains.

The Central Resources. A primary direction of computing throughout the world over the last two decades has been exploitation of the speed and capacity of large computers. These offer some economies of scale but more important, a vehicle for exploiting the expertise of systems programmers and powerful, versatile program packages.

Computer Center Improvements. The Computer Center Branch improved the systems software of its central DEC-10 and IBM-370 systems. The CCB completed the major transition of the 370 system to the new operating system (OS/MVS), increased the maximum amount of memory allowed for individual programs, and installed a new facility (MERCURY) for the automatic direct transfer of programs and data between the DEC and IBM systems. In conjunction with the Computer Systems Laboratory, CCB developed and installed a new facility (CLINK) for communication between the DEC-10 system and smaller computers at NIH by telephone line.

More work done, rates lowered. As in previous years there was a significant increase both in the number of central computing jobs processed and in the number of interactive computing sessions carried on through remote terminals... averaging about 50,000 more jobs and sessions per month than in FY'76. The combination of increased work done and systems improvements allowed two reductions during the year in charges for use of most of the computer center facilities. Overall, rates were reduced about 25%.

Data Management Tools. The Data Management Branch refined and expanded its tools for efficiently creating programs to meet the diverse data management needs of NIH scientists and administrators. This work continued on several levels. One of these, the RMAG project, uses the concept of a Recursive Macro-Actuated Generator, a programming language system to write programs that can generate programs in other languages. RMAG was used in FY'77 to create two new data management tools: (1) a symbolic logical retrieval system (SLR) that extends the ability to handle complex specifications for retrieval of records and (2) a highly versatile report generating facility. These are valuable additions to the existing DMB tools for creating, updating, reformatting, and querying files of computer records.

Statistical and Mathematical Packages. The Laboratory of Statistical and Mathematical Methodology (LSM) continued to provide support to NIH users for seven sets or packages of programs for statistical and mathematical analyses. Each went through at least one revision during the year. The use of these packages in FY'77 (almost 6000 accesses per month) was about twice that in FY'76, and the section that supports them answered over 3000 calls during the year. In addition, LSM completed and introduced a new package (C-LAB) for pattern recognition and cluster analysis and made improvement to its two packages for biomathematical modeling (MLAB and Modelaide).

Better Facilities for Image Display. The Computer Center provided improved facilities for manipulation and presentation of graphic images at remote video terminals and plotting devices. It installed a more powerful computing system linked to the DEC-10 system for the dynamic display of three-dimensional images such as macromolecular structures.

Image Processing Facilities. The DCRT tools for acquisition and analysis of biomedical images (eg, photomicrographs of cells and cell structures) were augmented. The division purchased a new "digitizer" that can automatically convert these pictures into computer processible information. Three existing programs (see project report on PEEP/DECIDE/GRAPH) for extraction, analysis and display of features from pictures were linked into a single system.

3

Clinical Care and Research. Computing at NIH has entered virtually every facet of the care of patients and analysis of data from clinical research studies. Four DCRT Branches and Laboratories (LAS, LSM, CSL and DMB) work with clinical investigators in the Institutes and with the Office of Clinical and Management Systems and other departments in the Clinical Center.

Patient Monitoring and Intensive Care. After five years of experience with the Surgical Intensive Care Unit for NHLBI, CSL worked this year with the NCI clinicians and the Clinical Center in the design of intensive care units that can serve both medical and surgical patients. For the cardiologists CSL also developed a prototype microcomputer system, capable of monitoring 35 ECG leads on a patient, to be used in a research study of therapy on patients with myocardial infarction.

Radiation Therapy. The CSL, in collaboration with the NCI Radiation Oncology Branch, is using computer assisted tomography to improve radiation treatment planning. The radio therapist examines the tomographic scan image at a video terminal to enhance features and to outline and select contours with a light pen. The image and a preliminary dosage schedule are then processed to determine expected dose distributions in the body. Research has begun on treatment optimization and the feasibility of computer controlled therapy machines.

Diagnostic Tools. Computer-based systems are now used at NIH to aid electrocardiography, pulmonary function testing, clinical laboratory tests, and nuclear medicine studies. Particularly noteworthy is the multi-year collaboration of CSL and LAS with the Clinical Center Diagnostic Imaging Department. This created, among other tools, so-called "heart movies" by a technique called ECG-gated scintigraphy. During FY'77 NHLBI investigators reported their work using this facility to examine heart wall malfunctions and got wide coverage in national papers and news magazines and was the lead item in an NIH report in the JAMA.

The computer programs of the nuclear medicine computer utility were extended and used for lung, kidney, gastric, cardiovascular and cerebrovascular studies. Subtle regional abnormalities can now be detected in the dynamic images of these organs recorded and analyzed by the computer system.

Data Storage and Retrieval. The power of computers to store and retrieve specific data and records is now being explored and exploited in a variety of clinical areas. This year CSL and DMB finished a system allowing the Pulmonary Branch, NHLBI, to send results from two different pulmonary function test systems via telephone line to the NIH central computers. Results from both sources are stored in a common file and can be retrieved by interactive query at a terminal in the pulmonary lab.

For the Cardiology Branch, NHLBI, DMB began a patient record system to include a broad range of information from physical examinations, ECG, x-ray, echocardiograms, catheterizations, angiograms and other examinations. On a larger scale, DMB improved and extended the capabilities of its Clinical Information Utility, which archives over a million test results each year from the Clinical Center Clinical Laboratories and can retrieve these in response to queries combining diagnoses, time, test type and test value.

Data Analysis. Analysis of data in clinical research combines the tools of file management and statistics and is guided by the interests, hypotheses and insights of the investigator in pursuit of a particular problem. Some of this can now be done by scientists using statistical packages directly through terminals in or near their offices. Other studies require the help of a statistician, and the LSM report this year includes a fascinating assortment of studies in such disparate areas as cystic fibrosis, coronary artery disease, cirrhosis, mental illness, sleep disorders, goiters, filariasis and the effect of smoking on polynucleotides in the blood.

Medical Modeling. Mathematical models are now common in preclinical research (biophysics, physiology, etc.). Their use in clinical medicine has been limited. The LAS has undertaken an examination of some existing physiological models and started collaborative work on improved models for pulmonary gas exchange with the Pulmonary Branch, NHLBI.

Laboratory Investigation. Laboratory investigation involves a great variety of instrumentation and often a large component of mathematical theory and model testing. There are nevertheless many data management tasks, particularly in large research projects, coordinating and analyzing the investigations of several laboratories.

Distributed Laboratory Microprocessors. The CSL began work on a prototype distributed Laboratory Data Acquisition and Control System (DLDACS). The system makes use of recent advances in small, relatively inexpensive computer processors and memories on single silicon chips. In the past few years CSL has used this microprocessor technology to build systems connected to single analytical instruments. The DLDACS system will use a network of remote microprocessors to link a variety of analytical instruments through a communications microprocessor to the existing H-516 computer that was used originally in the automation of NIAMDD laboratories in Building 2. The H-516 computer already has a link to the central DCRT DEC-10 system which now links to the IBM-370 system (see MERCURY above), providing a hierarchy of increasingly powerful computing capacity available as needed for larger and more complex computing tasks.

Nuclear Magnetic Resonance Spectroscopy. The DCRT and NIAMDD have collaborated for several years on the theory and application of Nuclear Magnetic Resonance Spectroscopy, a technique for examining the state of atoms within molecules and their relationships to one another. CSL helped set up computers to control the NMR instrument and receive and analyze data. The PSL and the NIAMDD Laboratory of Chemical Physics collaborated in performing experiments, interpreting results and developing new theory and experimental techniques. In FY'77 they examined two biologically active peptides angiotensin and bradykinin and developed a theory for optimal design of NMR experiments.

Correlation Function Spectroscopy. PSL scientists have developed and published the theoretical base for use of laser beam light scattering to characterize the mass movement of macro molecular and micro organisms. Current work focuses on the elastic coefficients of soft biological gels; eg, cytoplasmic gels, vitreous humor, collagen polymer networks and fibrin clots. Cooperating units include laboratories in NIAMDD, NIDR and NCI.

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Intermolecular Forces. The PSL conducts a continuing program of research on the theory of intermolecular forces in biological systems. This work has had application in collaborative studies within NIH and with scientists in other institutions in this country and outside the country. Studies during the year have dealt with electrostatic forces between cell membrane lipids and in collagen-polysaccharide mixtures and the binding specificity between pairs of macromolecules, such as immunoglobulin dimers and enzyme-inhibitor complexes.

Chemical Information Systems. The lead article in the January 21 issue of SCIENCE described the powerful Computer-Based Chemical Information Systems developed over a number of years by DCRT and NHLBI scientists in cooperation with chemists in this country and abroad. These systems also headed the two page list of computer-readable scientific data bases reported in the June issue of RESEARCH/DEVELOPMENT. One product of the DCRT project, an Atlas of Macromolecular Structure on Microfilm (AMSOM), makes the three dimensional views from a very powerful but expensive computer technique available at reasonable cost to scientists and students throughout the world.

Statistical Analyses and Mathematical Modeling. The consulting work of LSM with laboratory scientists at NIH covers virtually the entire range of bio-medical research from observations on living organisms to biochemical and biophysical investigations using pure materials or isolated preparations in vitro. The list of LSM collaborations this year includes a number of NIH investigators and projects that also have been working with CSL, PSL, and DMB. This provides, in passing, evidence of the utility of the original 1964 concept for the DCRT as an integrated central resource for all aspects of NIH information processing problems.

Testing Systems. For several years DMB has worked with the NCI and NIEHS to develop computer based systems for control of testing programs by monitoring of results of completed experiments carried on at laboratories separated geo-graphically and administratively. Last year DMB began a system for NIEHS to standardize day to day laboratory functions for mutagenesis experiments by providing interactive guidance to laboratory technicians. DMB finished the programming for the initial part of this project and NIEHS has written a con-tract to test the system in laboratories.

Administration and Program Direction. Management at NIH includes a remarkably wide span of functions in clinical, laboratory, and administrative areas. The Division of Research Grants and the NIH Office of Administration are respon-sible for central NIH administrative computer applications for grants, con-tracts, personnel, financial and materiel management. The DMB is the primary DCRT agent for developing applications for other parts of NIH, working whenever appropriate with CCB and LSM. Many applications created by DMB in previous years are now run independently by their "owners and operators" on the central NIH computers.

Data Base Systems. Over the last decade a major effort in computer science and technology has been on systems to handle complex data bases, i.e., files of records and items which are related to each other in a variety of ways. Pro-gress began in "business" areas where the item and record definitions are

usually reasonably well established. A number of Data Base Management Systems are now sold commercially some having so-called Data Base Communication Systems that allow use from remote terminals. In previous years CCB supported the IMS system for a few projects by contractors for the NCI and the Division of Financial Management. This year DMB became directly involved in the NIH Materiel Management System project, following the efforts of a consulting firm and a programming company. The MMS project collaboration includes working groups in DMB and CCB as well as the NIH Office of Administration. The first field implementation of MMS is scheduled for the first quarter of FY'78, if the procurement of terminals is not delayed.

NHLBI Extramural Information System. The NHLBI has been working to improve and integrate its systems that handle information for program direction and management. During FY'77 DMB worked with the Reports and Evaluation Branch, Division of Extramural Programs, to upgrade its systems that handle information on research grants and contracts for NHLBI. This project is an illustration of the periodic review and renewal required of all large administrative or "management" information systems in the NIH environment, where changes occur in both the organizational substance and procedures and the computer technology available to handle the information storage and processing needs.

Clinical Trial Cost Analysis. DMB helped the Division of Cancer Treatment, NCI, expand its file of cost information on clinical trials and preclinical drug screening to cover grants data as well as contracts. The system was finished during the year and is now run on a production basis by DCT/NCI.

Interagency Primate Program. The Division of Research Services wanted to improve procedures for reporting to the Interagency Primate Steering Committee from contractors managing primate breeding facilities. DMB provided computer programs (with editing facilities) to enable the contractors to enter their own data directly into the DRS file, thus speeding the quarterly reporting procedures.

PROGRAM BALANCE AND RESOURCE ALLOCATION

The DCRT mandate calls for an integrated program of service and research in support of NIH scientific and administrative activities. The DCRT has been a success because its six laboratories and branches function together as part of this integrated program, capable of finding effective solutions for the broad variety of information processing tasks at NIH.

During FY'77 more than forty of the DCRT professional staff worked with one or more of their counterparts in another DCRT laboratory or branch on projects requiring combined expertise. Each laboratory and branch worked with and supported all the others. This complex web of interactions extends outward from DCRT to all other NIH Bureaus, Institutes, Divisions and Offices and to scientific and technical groups outside the NIH.

This balanced DCRT program of activities includes services, consultation, collaboration, research and development as well as education and information resources. Without the other activities, computer facilities and programmers alone will not meet the NIH needs for computing.

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Program balance and resource allocation have, over the last decade, become problems throughout NIH. Congressional Mandates and Presidential Initiatives come interspersed with new calls for efficiency and economy and regular cuts in NIH employment ceilings, as well as with periodic requests to increase the output of "relevant" science and to speed the transfer of knowledge through technical consensus and technology transfer to improve health care for the Nation.

The following figures show one aspect of the problem for DCRT:

	FY'69	FY'77	Change
Computer Center Work (millions of jobs & sessions)	0.3	4.2	+1300%
DCRT Positions	316	251	-21%

(The positions counted here are "hard" positions and do not include positions on loan from other organizations.)

The vast increase in computer center work has been made possible by improved computer systems allowing more work done by fewer people attending their operations. At the same time, however, the complexity of the new systems requires more expertise and more people on the systems teams which design and maintain the computer systems and more in the technical information and user assistance sections.

By hard work, judicious management and some borrowing of positions from other organizations, DCRT has maintained approximately a 2 to 1 ratio of "service" oriented staff to "research" personnel over the entire period. The fact is, however, that program balance has suffered markedly at times. As a result of the continuing personnel cuts through FY'74, one laboratory was disbanded and the other laboratories lost positions. The new wave of retrenchment breaking over NIH in FY'77, with more promised in coming years, poses a very serious problem for DCRT.

THE FUTURE

DCRT Plans. The DCRT plans to continue as much as possible in the successful directions it has pursued in previous years. This will be difficult.

Early this year the DCRT submission to the NIH Forward Plan process asked for a few positions in FY'79 to (1) strengthen specific areas of computer technology, statistics, mathematics and engineering, and (2) to recruit some staff fellows or visiting associates as the "linking agents" to exploit applications in new medical and scientific areas.

These hopes receded a few months later when DHEW reduced the current (FY'77) NIH employment ceilings (DCRT's share, minus 10), promised more cuts in FY'78 and apparently gave low priority to the NIH in the Zero-Based Budgeting for FY'79.

The DCRT plan is now to husband its financial and human resources and continue its perennial struggle to maintain morale in and balance among the essential nuclei of scientific and technical competence. Expansion into new substantive application areas will depend primarily on collaborative projects with the staff of other NIH Bureaus, Institutes and Divisions without the benefit of new "linking agents" in DCRT.

In the middle of the year the General Services Administration indicated its intent to press again for "recompetition" of the central NIH computer systems. In the extreme this would mean starting off with a new brand of computer hardware and rebuilding a central capability comparable to that developed by DCRT over the last ten years. This would be a giant setback to computing at NIH.

The Larger Perspective. There are three apparent contradictions in the picture of computing at NIH. One of these relates to attitudes and actions in other parts of the Federal government, including those discussed in the previous section.

  ° Computing has flourished in the NIH programs because of a conscious NIH commitment in the mid 1960s to the intellectual and technical resources essential for good computing and cost-effective computing results... but larger Federal pressures to contain personnel costs and curb poor quality computing performance by regulation appear destined to cut deeply into that scientific and technological base and to decrease the quality and effectiveness and eventually to increase the cost.

The other two contradictions are found within NIH and in the national academic and scientific community.

  ° Computers on the NIH campus are more accessible, reliable, powerful and widely used than ever before... but as a result some NIH scientists and administrators have relatively less comprehension of the nature of the NIH computing systems, their capabilities and limitations, benefits and costs, care and feeding, and this sometimes impedes the effective application of information processing techniques for the conduct and support of biomedical research.

  ° Computing at NIH is alive, robust and maturing... but in March the chairman of an active academic department of computer science, working in biomedical applications of computing, wrote to several people at NIH and other academic departments lamenting the lack of a clear focus and overall policy at NIH for the application of computer science, particularly a policy that would deal with the biomedical research/health care "interface" or boundary.

Common to all three contradictions is a lack of understanding of recent developments (especially in the last five years) in computer science and technology or a lack of agreement about the significance of these developments for the conduct and management of biomedical research and its support mechanisms.

The matter of communication with and transfer of computing technology to the NIH scientific and administrative staff is clearly a primary responsibility of DCRT. The matters of policy and communication with other parts of the Federal Government and with the academic and scientific community, will require a cooperative effort between DCRT and the Office of the Director, NIH, and other programs at the NIH.

These problems for computer research and technology are similar to some faced by NIH with respect to biomedical research and technology. Both areas have become vastly more complex over the last 30 years. Both come into the public view in isolated bursts of news about technical coups, social costs, ethical concerns, or managerial catastrophes. These glimpses raise hopes and fears, create expectations, but do little to create useful understanding.

The future of computing at NIH will be determined largely by the understanding of computing by the NIH, its workers and its leaders. The summaries of the DCRT Laboratories and Branches in this Annual Report provide an excellent opportunity to gain greater insight into the breadth and depth of computing at NIH.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT

2. OFFICE OF ADMINISTRATIVE MANAGEMENT

3. L. Lee Manuel
    Chief

I. SUMMARY

Function

The Office of Administrative Management, under the direction of the Executive Officer, provides administrative, financial and personnel functions to support the Division's programs. The office serves as liaison to these functions with the NIH Office of Administration and other OD, NIH offices.

Scope of Activities

The office handles the usual range of administrative managerial functions for an NIH research division of almost 300 people. In addition our Financial Management/Project Control Sections is currently tracking 1,795 project accounts involving 5590 registered users of the DCRT computer facilities and services. These services have grown to an estimated $25,000,000 in FY 77. This increase has been handled with no increase in staff. Requisitions, contracts and other documents are processed by the Administrative Services Section and covers a variety of procurements of approximately $15 million.

Highlights of Years Activities

Several new activities arose during the year. First, the Personnel Section, in compliance with Civil Service Commission and DHEW directives, began a comprehensive position classification review of all positions over a three year span. Second, DCRT took part in the NIH Forward Plan process for the first time. To support the necessary program planning, this required the development of a large budget "package" in addition to the preparation of the standard Budget and Workload/Manpower exercises. Third, the Secretary's initiatives for correcting major deficiencies in the contracting and grant process added a substantial new load of reporting requirements for the Division.

The Administrative Services Section conducted a comprehensive revision and update of all of the DCRT Policy and Procedure Statements. Major space and renovation planning was started for Building 12 and 12A. The office also worked closely with the EEO Coordinator in providing data to allow assessment of Affirmative Action to DCRT and to assist her in preparing the Affirmative Action Plan.

Future Plans

The coming year should include major moves and renovations with
Buildings 12, 12A and 12B. These will allow consolidation of some
currently scattered DCRT staff and more unified services for DCRT
clients. There will undoubtedly be new administrative managerial
requirements and modifications of old ones forthcoming from the NIH,
the PHS, the Department, the GSA and the Civil Service Commission.
The recent cuts in DCRT personnel ceilings as part of the NIH cuts
mean that this office and the Division will have to do more with
fewer human resources.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT

2. OFFICE OF ADP POLICY
    COORDINATION

3. Henry J. Juenemann
    Chief

I. SUMMARY

Function

The Office of ADP Policy Coordination, under the direction of the
Assistant Director of the Division, has two closely related functions.
It serves as:

. a focus for NIH-wide coordination of automatic data processing policy
   matters.

. a central NIH point of contact with the Public Health Service, the
   Department of Health, Education and Welfare, and other HEW agencies,
   the General Services Administration and the Office of Management and
   Budget on policy questions and NIH's participation in policy
   development.

Scope

The office provides advice and assistance about internal DCRT operations
and coordinates DCRT's ADP policies and activities with those of other
agencies. This includes advising the Director of DCRT and through him
the Director of NIH on ADP policy matters, assisting the NIH Division of
Management Policy on questions relating to its responsibility for
administrative computer applications, reviewing and evaluating proposals
from NIH B/I/D/O's for ADP and computing procurements and contracts,
directing the development of the annual NIH ADP Plan, representing the
NIH in PHS and DHEW policy formulation efforts, working with GSA and OMB
staff on procurements, coordinating Interagency Agreements with other
Federal agencies that use DCRT facilities, and answering inquiries from
scientists and administrators who are confused by the whole process.

Highlights of the Year's Activities

The annual ADP Plan, required by DHEW was again completed. This
management process, involving an opportunity for all B/I/D/O's to take
a two year forward look at projected ADP efforts necessary to support
their research or research management programs showed a 43 million
dollar, 574 man-year ADP program in place during Fiscal Year 1977
growing to 49.5 million dollar and 620 man-years by Fiscal Year 1979.

Particularly in the early part of the fiscal year, OMB placed emphasis on contracting with private industry to meet government ADP needs. In Fiscal Year 1977 14.8 million dollars was used by NIH to obtain ADP services from the private sector with an additional 22.8 million dollars flowing into the private sector for equipment, supplies and other hard goods.

In the process of monitoring the policy implications of this program and assuring conformity to existing OMB, GSA and Department regulations, 125 proposals for ADP equipment or services were reviewed during the period between July 1, 1976 to September 30, 1977.

The effort to obtain GSA approval to issue a competitive solicitation for editing display terminals spanned 18 months and consumed many hours of work by this office and Computer Center Branch, DCRT. This was due partially to the delicacies injected as a result of a previous protest to GAO on a similar situation, partly as a result of GSA ADP procurement procedures and partly due to the technical complexities of NIH's requirement for editing display terminals.

A total reprocurement of NIH's main central computing facility 370's has been mandated by GSA. A briefing for industry was conducted in the latter half of the year. At year's close the strategy for the recompetition is being worked out with GSA. In reviewing proposals for contracts or equipment acquisitions, this office is very fortunate in being able to call on the consultive expertise of the other labs and branches of DCRT. During the year they were extremely helpful in insuring technical merit is part of the review process.

Future Plans

Federal ADP policies and requirements are becoming increasingly complex as OMB, GSA, DHEW and PHS become more and more involved. As a result, the office must expect to spend an increasing portion of its available man-hours in attempting to guide policy development in productive directions and in meeting regulatory requirements. The office will continue to work to spare large numbers of NIH research and research support staff members the task of becoming expert in the many nuances of ADP-related regulations. However, it is anticipated that the full recompetition effort for the NIH computer center will consume most of the resources of this office during the upcoming year and will in addition, require extensive assistance from OD and CCB staff.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT

2. OFFICE OF SCIENTIFIC AND   3. William C. Mohler, M.D.
    TECHNICAL COMMUNICATIONS   Chief

I. SUMMARY

Function

The DCRT Office of Scientific and Technical Communications, under the direc-
tion of the Associate Director of the Division, includes three areas of
activity:

  ° The DCRT Information Office deals with a range of "publics" interested
    in or affected by DCRT activities but most of its efforts are now aimed
    at providing information to NIH employees.

  ° The DCRT Library maintains a special collection in computer science
    and mathematics and related areas in statistics, engineering, infor-
    mation science, and management. Information resources and services
    support DCRT activities and provide additional support for other NIH
    personnel. The DCRT Library also functions as part of the local net-
    work of special libraries to maximize services by sharing resources.

  ° Biomedical Image Processing and Decision Analysis, encompassing research
    projects and advice and consultation to scientists at NIH and other
    organizations.

HIGHLIGHTS OF YEAR'S ACTIVITIES

The Information Office

The new DCRT Information Officer, Mr. Paul Hudson, came on board at the be-
ginning of FY 77. Two projects were left from FY 76.

1. He convinced the NIH print shop and the GPO to require a successful
    reprinting of "Computing at NIH, Tools for the Advancement of Medicine"
    which had come from the GPO contract printer as a total disaster.

2. He completed the preparation of DCRT '76, a publication for visitors
    and others interested in a synopsis of the division's FY 76 work.

In collaboration with the Chief, OSTC, and other DCRT staff, he began to
develop the framework for a division Information Program. The DCRT leadership
reached a preliminary consensus of priorities for DCRT communication with
several "publics" within NIH (eg, existing computer users, potential users,
NIH "Top Management," and B/I/D/O scientific and administrative leaders) and
outside NIH (eg, scientific and technical peers of DCRT staff, Federal agencies
concerned about NIH computing and the General Public).

The plan to start implementation of the program during FY 77 included work on:

○ A complete revision of the DCRT Services and Facilities handbook.

○ A series of articles for the NIH Record and the Computer Center Branch Interface to highlight ongoing projects.

○ A set of pamphlets and slide shows on specific DCRT Laboratories, Branches and computing facilities of broad interest to NIH employees.

○ A set of seminars for NIH scientific and administrative leaders to create better understanding of DCRT, its services and the scientific and technical expertise it offers for collaborative projects.

During the year the Information Office also answered several hundred inqueries and requests for publications as well as for slide shows, movies and tours of the NIH Computer Center. The office provided editorial advice for DCRT employees and began several internal division information distributions.

The DCRT Library

Library Services. Library users include the DCRT staff, which currently totals about 280 full-time employees, and users from other parts of NIH and the federal government. This year more than 100 new outside users registered to borrow from the collection.

During FY 77 monograph loans again totalled about 2000. There were over 500 interlibrary loans for our Library users and in response to other libraries. The need to share resources among libraries continues to grow every year.

The Collection and Equipment. Acquisitions include over 200 monographs, 150 documents (reports and theses), and 170 serial subscriptions in FY 77. With the aid of Library Committee members and other DCRT staff, the continuing review of the collection resulted in further weeding of outdated or seldom used materials.

A microfiche reader is now available for the growing number of reports and journals which the Library is acquiring in this format.

Cooperative Efforts with Other Libraries have resulted in a wide range of improved library operations and information services.

1. The DCRT Library participates in FEDLINK, a computer network administered through the Federal Library Committee. The Ohio College Library Center (OCLC) cataloging data base has significantly reduced the time and labor involved in cataloging and card production. Card orders are filled within one to two weeks and the card production capability has enabled us to increase cross references to the document collection. Previously, delays on Library of Congress card orders ranged from three weeks to fifteen months.

   The OCLC data base has also been the locator for approximately 45 percent of our interlibrary loans this year, providing much faster service for the users.

2. The Library's membership in the Interlibrary Users Association (IUA) also facilitated interlibrary loan operations. Forty percent of our loans were obtained from other member libraries of IUA.

3. In April, the DCRT Library joined other federal libraries in a group subscription to Bibliographic Retrieval Services, Inc., (BRS). This vendor supplies nine computerized data bases via Telenet. The <u>Computer and Control Abstracts</u> and the <u>National Technical Information Service</u> data bases are of particular interest to DCRT for reference and/or acquisition. BRS software also provides additional search strategies when accessing NLM's MEDLINE.

Image Processing and Decision Analysis

A new research project involved derivation of a general differential equation for monotonic growth phenomena that subsumes prior models as special cases and affords greater flexibility in curve fitting. Two other research projects extended previous work using computers to characterize microscopic images of cells and cell nuclei by objective measures and to extract reliable criteria for discriminating among different categories (such as normal and malignant.) A fourth project involved improvement and application of a computer system (PEEP-DECIDE-GRAPH) developed to facilitate analysis of digitized microscopic images and medical decision making.

<u>Advice and Consultation.</u> These activities of J.M.S. Prewitt during FY 77 included work with the following groups:

° The National Cancer Institute Committee for Cytology Automation, the Diagnostic Radiology Advisory Committee and the NCI Breast Cancer Task Force.

° The National Heart, Blood and Lung Institute.

° The National Science Foundation (NSF): RANN, the Division of Computer Research and the Division of Engineering.

° Membership in the U.S./Japan Cancer Cooperative Research Program on Cytology, the NBS/EIA/IEEE Committee on Image Data Bases, the NSF Inter-Agency Panel of Medical Physics, the NSF Committee on Transportable Software for Image Processing, the NSF Automation Research Council and chairmanship of the NSF Committee on Ultrasonic Tissue Signatures.

° The IEEE Machine Pattern Analysis Group and its subcommittees on Image Processing and Scene Analysis, Data Bases and Biomedical Pattern Recognition.

Mrs. Prewitt was a visiting lecturer for the Society for Industrial and Applied Mathematics (SIAM) on topics related to image processing and decision analysis and an associate editor of "Computer Graphics and Image Processing."

PLANS FOR FY 1978

The Library looks forward to increased space to help the shelving overflow and improved user reading areas. It will review its document collection with respect to current relevance and needs. Information about the Library's services and resources will be described on a continuing basis with the Library's Monthly Acquisitions List and in DCRT Highlights. The staff also plans to maintain a bulletin board in the new entrance lobby of Building 12A to provide better visibility of new acquisitions and services for all DCRT employees and computer users.

The Information Office plans for FY 78 will center around further refinement and implementation of the basic DCRT Information Plan and evaluation of its effectiveness. This may lead to revision of the current priorities in the plan.

Procurement of a new digitizing scanner by DCRT as a service facility should provide new opportunities for collaborative work and research projects in image processing.

II. PROJECT LIST

1. Tumor Growth Curves. J.M.S. Prewitt, OSTC.

    A generalized differential equation has been developed to help with the problem of describing tumor growth that do not fit classical growth models.

2. Cell and Tissue Images. J.M.S. Prewitt, OSTC.

    This is a long-term project to characterize and analyze quantitatively, images of cells and cell components in tissue and sections. Cell and tissue images come from collaborative investigation. Digitized images are analyzed using the PEEP/DECIDE/GRAPH system in DCRT.

3. PEEP/DECIDE/GRAPH. J.M.S. Prewitt, S.C. Wu, OSTC.

    PEEP/DECIDE/GRAPH is an interactive programming system written in SAIL, the Stanford Artificial Intelligence Language, and operating on the DCRT PDP-10 computer. PEEP is designed for picture processing applications, DECIDE is intended for algorithmic decision-making and exploratory data analysis, and GRAPH has capabilities for two and three dimensional graphics. PEEP/DECIDE/GRAPH has been implemented as a single system with a large library of image processing, feature extraction and decision-making algorithms. We are maintaining it for public use as well as using it for our own research on blood cells, breast aspirates and bladder epithelium.

4. The DCRT Information Program. This was a new project undertaken to specify the needs and priorities for specific kinds of information directed to specific "publics" within NIH and to groups outside NIH with an interest in biomedical computing activities. During FY 77 a preliminary framework was developed, existing publications were revised and several new projects were started to describe specific DCRT activities within its Laboratories and Branches.

5. Revision of the DCRT Library Circulation System. For several years the DCRT Library has used an automated circulation system developed for the EPA. During FY 77 a number of alternative hardware/software improvements were examined including a microcomputer in the library. The cost of system development suggests that any revision in the forseeable future will be a modification of the existing system.

PUBLICATIONS AND PRESENTATIONS

Prewitt, J.M.S., Decision Theoretic Approaches to White Cell Differentiation. In "Decision Making and Medical Care: Can Information Science Help?", F.T. deDombal and F. Gremy, Editors, North-Holland Publishing Company, Amsterdam, 1976, pp287-308*.

Prewitt, J.M.S., Pattern Analysis Applied to Cell Images. Brown University, February, 1977.

Prewitt, J.M.S., Image Processing and Pattern Recognition. Cornell University, March, 1977.

Prewitt, J.M.S., Data Bases: Formats and Standardization. Second International Conference on Automation of Cancer Cytology and Cell Image Analysis. Tokyo, May, 1977.*

Prewitt, J.M.S., Mathematical Methods Applied to Image Processing in Medicine. First World Conference on Mathematics at the Service of Man. July, 1977. Barcelona, Spain.*

Prewitt, J.M.S., Computer Assisted Identification of Cell in Needle Aspirates of Mammary Tumor, Medinfo '77. Toronto, August, 1977.*

Prewitt, J.M.S., Prospective Medical Advances in Computerized Tomography. Symposium on the Basicranium, J. Bosma, Editor, U.S. Government Printing Office. in press, 1977.*

Wu, S.C., Application of the acta-scanner in the radiation (Co) therapy for body inhomogeneities. In proceedings of The 29th Annual Conference on Engineering in Medicine and Biology, Boston, Mass., November 6, 1976.

Huang, H.K., Wu, S.C., Ledley, R.S., Evaluation of the mass density distribution of the human body in vivo-theoretical aspect. In proceedings of the 29th Annual Conference on Engineering in Medicine and Biology, Boston, Mass., November 6, 1976.

*Printed Papers

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER
		Z01 CT 00029-02 OSTC

PERIOD COVERED
July 1, 1976 - September 30, 1977

TITLE OF PROJECT (80 characters or less)

Bladder Cancer Image Processing

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Judith M.S. Prewitt

COOPERATING UNITS (if any)
St. Vincent Hospital, Worcester, Mass.

Jet Propulsion Laboratory, Pasadena, Calif.

LAB/BRANCH
Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION
DCRT/NIH

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.30	0.25	0.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☒ (b) HUMAN TISSUES   ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The long range goal of this project is to quantitively characterize the epithelium of human urinary bladder from scanned digitized images of stained histologic sections using digital computers, and to develop a data-directed taxonomy for the range of tissues from normal to invasive carcinoma. The PEEP-DECIDE-GRAPH system was used to analyze the digitized images. The object extraction methods met with varying degrees of success, depending on the quality of the tissue sections. A new algorithm for shape and orientation assessment, based on a complex number representation of position along a boundary, was developed and applied.

PHS-6040

Bladder Cancer Image Processing

The long range goal of this project is to quantitatively characterize the epithelium of human urinary bladder from scanned digitized images of stained sections using digital computers and to develop a data-directed taxonomy for the range of tissues from normal to invasive carcinoma.

This project, inactive during the previous fiscal year, was reactivated with the change in programming staff.

The data base was not altered and consisted of images of tissue sections. Tissue sections were prepared on microscopic slides at St. Vincent Hospital, Worcester, Mass. and stained with hematoxylin. They were scanned at the Jet Propulsion Laboratory, Pasadena, Calif. so that the resulting images were at 630X, sampled at half micron intervals and rendered in 256 linear grey levels. The material was routine clinical preparations of variable and sometimes mediocre quality. The absorption peak for the tissue sections was determined to be at 570NM and all scans were made at both this wavelength and in white light. In one experiment with tissue sections stained with gallocyanin chromalum, the response in the entire visible range was assessed.

The PEEP-DECIDE-GRAPH system was used to analyze the digitized images. (In fact, the project was the impetus for implementing that system, which is discussed in a separate project report). All of the object extraction methods were applied to digitized images of tissue sections. They met with varying degrees of success and depending on the quality of the tissue sections, one or another method may be necessary.

Two morphologically distinct tissue sections were chosen for in-depth study. Both yielded to thresholding for obtaining nuclear images. The entire armamentarium of PEEP features was extracted on approximately 20 nuclei from each tissue. Linear and quadratic discriminant analysis were used to learn each tissue section as a category. Specimens from each tissue were then classified with the following result of demonstrated internal consistency: nuclei in one tissue type were overwhelmingly more like each other than like cell nuclei from other tissue types.

A new algorithm for shape assessment, based on a complex number representation of arc length along a boundary, was developed. All concavities can be found and the area between each one and the subject curve measured. In addition, the orientation of the object under study can be obtained from the Fourier coefficients. The technique was applied to blood cells and bladder epithelium nuclei for test purposes. A manuscript has been prepared for publication.

The data directed classification of tissue sections might well be an improvement over current subjective and often dubious decisions. The difficulty of the undertaking should not be under emphasized. Classification using algorithms may lead to greater objectivity, public verifiability, and greater consistency. There is always the opportunity for discovering new significant differences in optical properties between papillomas and papillary carcinomas using the digital computer.

At the present time, the project has been reactivated and will remain so, especially if suitable tissue section material becomes available.

22

PERIOD COVERED
July 1, 1976 – September 30, 1977

TITLE OF PROJECT (80 characters or less)

Characterization of Cells from Breast Aspirates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Judith M.S. Prewitt

COOPERATING UNITS (if any)

Academic Hospital, Uppsala, Sweden

LAB/BRANCH
Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION
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TOTAL MANYEARS: 0.20	PROFESSIONAL: 0.20	OTHER: 0.00

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☒ (b) HUMAN TISSUES   ☐ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The long range objective of this project is to characterize images of cells from human breast aspiration biopsies, and to distinguish malignant from benign cells. Using the PEEP-DECIDE-GRAPH system, cell images were displayed and thresholded, and eighteen numeric characterizing features were extracted for each of approximately 100 cell nuclei. Using quadratic discrimination, combinations of as few as four features and in many cases just one feature allowed near perfect discrimination between cell categories. The project will continue along lines that would lead to a grading system for breast cells.

PHS-6040

Characterization of Cells from Breast Aspirates

The long range objective of this project is to characterize images of cells
from human breast aspiration biopsies, and to distinguish malignant from
benign cells. Aspiration biopsy is used widely in Europe but not in the
United States.

Biopsy material was prepared at the Department of Clinical Cytology, Academic
Hospital, Uppsala, Sweden, stained with Papanicolau stain and scanned there,
digitized and recorded on magnetic tape. The Uppsala scanning microscope has
7/10 micron square aperture and has a moving stage and records 256 grey levels.
Using the PEEP system, cell images were displayed and thresholded. This
generated objects which were subjected to feature extraction using the PEEP/
DECIDE system. Eighteen numeric characterizing features were extracted for
each of 100 cell nuclei in five cell categories. Examples of these features
are area, average brightness, average chord, entropy, kurtosis and skewness
of the optical density histogram, density, variation in brightness, variation
in chord length and variation in diameter.

Each of four categories of benign cells was distinguished from the category
of malignant cells. Using quadratic discriminations, combinations of as
few as four features and in many cases a single feature allowed perfect dis-
crimination between pairs of cell categories. Useful features included
skewness of the optical density histogram, nuclear area, length of major
axis, density and entropy.

A manuscript, "Computer Assisted Identification of Cells in Needle As-
pirates of Mammary Tumors," has been accepted for presentation at MEDINFO '77
and accepted for publication in the Proceedings.

The practical significance of this research lies largely to developments in
the automation of cytologic examinations. The project will be continued both
in the United States and Sweden using more carefully scanned cells prepared
with gallocyanin chromalum.

PERIOD COVERED
July 1, 1976 - September 30, 1977

TITLE OF PROJECT (80 characters or less)

Other Applications of PEEP/DECIDE/GRAPH

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Judith M.S. Prewitt

Dr. S.C. Wu

Dr. R. Brooks, National Institute of Neurological and Communicative Disorders

Dr. K. Kent, National Heart and Lung Institute

Dr. H. Lee, Computer Systems Laboratory, DCRT

Dr. T. Pavlidis, Princeton University

COOPERATING UNITS (if any)

Princeton University, Princeton, N.J. Dept. of EE

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INSTITUTE AND LOCATION
DCRT/NIH

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.65	1.50	0.15

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

PEEP/DECIDE/GRAPH is an interactive programming system written in SAIL, the Stanford Artificial Intelligence Language, and operating on the DCRT PDP-10 computer. PEEP is designed for picture processing applications, DECIDE is intended for algorithmic decision-making and exploratory data analysis, and GRAPH has capabilities for two and three dimensional graphics. PEEP/DECIDE/GRAPH has been implemented as a single system, ILAB. A large library of image processing, feature extraction and decision-making algorithms has been built. We are maintaining ILAB as a public utility, as well as using it in our own research on blood cells, breast aspirates and bladder epithelium.

Other Applications of PEEP/DECIDE/GRAPH

PEEP/DECIDE/GRAPH is an interactive programming system written in SAIL, the Stanford Artificial Intelligence Language, and operating on the DCRT PDP-10 computer. PEEP is designed for picture processing applications, DECIDE is intended for algorithmic decision making and exploratory data analysis, and GRAPH has capabilities for two and three dimensional graphics. The system was originally written for the NCI Bladder Cancer Image Processing Project but is of wide utility. We will continue to make PEEP/DECIDE/GRAPH available for public use.

In the PEEP system and appendages to it, objects can be obtained from optical density histograms. This option is available in global and local form. Derivatives, Laplacians, Hueckel and other edge detection operators can be applied. A large library of feature extraction algorithms has been built. These features encompass numeric descriptions of size, shape, content, contrast, comparison and orientation. Examples of such features are area, average brightness, diameter, average chord, entropy, kurtosis and skewness of the optical density histogram, integrated optical density, variation in brightness, variation in chord length, variation in diameter, Fourier coefficients of a boundary, bending energy, medial axis transforms, major axis and minor axis.

DECIDE enables the performance of parametric and non-parametric recognition of objects. Linear and quadratic discriminant analysis form the basis for parametric recognition. Coefficients of the best discriminant function can be learned from exemplary objects using a learn command. New test objects can be classified into a learned category using the classify command. The user has control over various parameters of the learning process. For example, likelihood maximizing discriminant functions can be developed. Non-parametric recognition is performed by the cluster command. Again, many variations of data normalization, cluster merger strategy and cluster type emphasis are available.

GRAPH allows the user to create and display graphic structures in two and three dimensions and to use different vantage points for viewing them.

The three subsystems were merged into one and PEEP data formats were change to be compatible with MLAB. In addition, the Fourier analysis of curves a GRAPH have been incorporated into MLAB.

In conjunction with Dr. R. Brooks at the National Institute of Neurologica and Communicative Disorders and Stroke, PEEP was used to obtain and manipu late EMI two dimensional cross sectional reconstructions of the human head Special data conversion programs were written to format data so that PEEP could be used. It is envisioned that one early application will be image subtraction.

In collaboration with Dr. K. Kent at the National Heart and Lung Institute a project was continued in order to make use of the decision making capabi ties of DECIDE. An on-line expandable data retrieval system had been designed for the purpose of compiling data on the natural history of patien with coronary artery disease. Data on 200 to 300 patients over a period two years will be collected and entered by means of a special questionnair A general purpose input program for composing questionnaires leading to di structures compatible with DECIDE had been written. Decision making logi

will be developed so that a prospective diagnostic scheme can be obtained. From time to time graphic display is necessary. This project is similar but more elaborate than another National Heart and Lung Institute collaborative program designed to study pre and post-operative factors indicative of surgical risk.

In collaboration with Dr. H. Lee, CSL/DCRT, PEEP was used to manipulate EMI scanner reconstructed body cross-sections as part of a project to link computerized tomography with radiation treatment planning.

In collaboration with Dr. T. Pavlidis at the Department of Electrical Engineering of Princeton University, a project was conducted to apply linear polygonal segmentation to the nuclear and cell boundaries of normal human leukocyte images. The segmentation algorithm was improved. A grammar for cell and nuclear boundaries has been devised. Features of the polygonal boundary approximation can now be used for characterization.

PERIOD COVERED
July 1, 1976 – September 30, 1977

TITLE OF PROJECT (80 characters or less)

Tumor Growth Curves

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Judith M.S. Prewitt

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION
DCRT/NIH

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0.00

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☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A new second order non-linear differential equation for monotonic growth is proposed. This equation contains all classic models such as the Gompertz, logistic and exponential as special cases, and introduces an infinity of intermediate curves with varying inflection points. The solutions to the growth equation are obtained in closed form, and can be expressed in a time-free form which allows inter-comparison of the shape of different growth curves independent of age and dependent only on tumor extent. Numerical solution of equations to fit the general growth curve to data is unique. This equation should facilitate comparing data from different laboratories and provide an intrinsic characterization of the growth phenomena.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities   1. DCRT

2. LABORATORY OF APPLIED STUDIES   3. Eugene K. Harris
                                                    Chief

I. SUMMARY

Function

The Laboratory of Applied Studies (LAS) has three main purposes:
. in collaboration with biomedical scientists, to apply
mathematical theory and computing science to the construction,
testing and improvement of mathematical models of physiological
processes, particularly dynamic flow processes, transport of
substrate to tissues and macromolecular interactions;

. in collaboration with clinicians, to develop and apply
mathematical or statistical theory and computer programming to
improve diagnosis of disease and assessment of treatment;

. to engage in independent research in applied mathematics,
statistics and computer systems necessary to provide a sound
theoretical basis for collaborative studies.

LAS consists of two sections in addition to the Chief's office:
1) Applied Mathematics Section (J. E. Fletcher, Ph.D., Head),
including specialists in applied mathematics, numerical analysis,
computer science, mathematical physiology; 2) Medical Applications
Section (J. J. Bailey, M.D., Head), including physicians, electronic
(biomedical) engineers, computer systems analysts. The chief, LAS,
is a biostatistician.

Scope of Work

The Laboratory of Applied Studies works on a variety of projects
in basic and clinical biomedical science. In large part these
are carried out in collaboration with other groups at NIH and
elsewhere in the U.S. and abroad. The collaborating investigators
this year included:
. biochemists and pharmacologists - at U. of Iowa, Northwestern U.
   and other universities, NHLBI, Naval Research Laboratory,
   V.A. Hospital (Hines, Illinois) and elsewhere, working on
   drug-protein binding problems,

- physiologists - in the U.K. and Germany studying the transport of substrate through the microcirculation,

- clinicians - at NIH in the cardiology and pulmonary branches of NHLBI,

- clinical chemists and pathologists - in California, elsewhere in the U.S., and in the U.K., engaged in the collection of reference values in laboratory medicine,

- electrocardiologists (and governmental agencies) - in the U.S., Canada and Europe concerned with the evaluation of computer-based ECG interpretation.

During FY 77 LAS staff members participated in various teaching and consulting (or advisory) activities: Teaching - J. Fletcher: Advanced calculus (FAES), Data analysis in macromolecule-ligand binding studies (DCRT seminar series); E. Harris: Analysis of time series of clinical data (DCRT seminar series). J. Bailey was a member of several site-visiting teams for NHLBI concerned with computer analysis of exercise ECG s, biophysical studies in pediatric cardiology and studies in cardiovascular pathology. E. Harris continues to be a consultant in applied statistics to the Food and Drug Administration's Division of Medical Devices and Diagnostic Products. He has also served as an invited speaker at seminars of the College of American Pathologists concerned with applications of statistical theory to problems facing clinical laboratories.

Some highlights of LAS program activities during FY 77

1. Generalized mathematical model of equilibrium-binding data: A generalized mathematical model has been constructed that includes the well-known (but often mis-used) Scatchard model of drug-protein binding as a special case, but may also represent the Stepwise Equilibrium model derived previously. This new model is simpler to fit than the Stepwise model, yet is not restricted to the Scatchard assumption of independent, noninteracting binding sites. It is therefore appropriate for the analysis of all equilibrium binding data. Fitting to published data has revealed that many earlier analyses purporting to interpret macromolecule-ligand binding properties were probably faulty because of incorrect use of binding models.

2. A new programming system for analysis of scintigraphic data: The Extended Nuclear Utility (ENU) programming system is an example of the specialized software systems developed from time to time within LAS to meet the needs of collaborative projects.

Operating on the LAS minicomputer in the Diagnostic Imaging (formerly Nuclear Medicine Department (CC), ENU is a modular system which runs at almost the speed of a Fortran batch program but offers the user power to interact with and modify program statements. Modular routines for data collection, image construction and image display are included. Use of the ENU system has greatly reduced the programming time necessary to generate desired analyses of cardiac, pulmonary or renal scintigraphic data; for example, imaging of both temporal and spatial information to describe the functional state of an organ system.

3. Mathematical modeling of pulmonary gas exchange:
In this project, mathematical modeling of ventilation-perfusion in the lung (V/Q) is proceeding concurrently with empirical estimation of regional V/Q ratios from scintigraphic data collected in over 300 pulmonary patients. Currently, the Kelman method for computer-generation of O_2-CO_2 diagrams has been implemented on the PDP-10 and the minicomputer system in the Diagnostic Imaging Department, CC. However, the Kelman method and models of V/Q distribution in the current literature based on this method (e.g., the West-Wagner model) involve many doubtful assumptions and use inefficient numerical methods. Improved methods are under development which, when combined with data from ongoing pulmonary laboratory studies, will provide a better quantitative description of pulmonary pathophysiology on a regional basis. These results should aid in diagnosing and understanding the evolution of lung diseases involving ventilation-perfusion mismatch.

II. Annotated list of LAS projects

Mathematical modeling of biological processes:
J. Fletcher (LAS), A. Spector (University of Iowa): Development and application of mathematical models and numerical methods in studies of binding equilibria, substrate transport in the microcirculation, diffusion processes in physiology.

Simulation of physiological systems: E. Hill, J. Fletcher, E. Harris (LAS); C. Tidball (George Washington University). Exploration and testing of computer programs simulating responses of physiological systems to determine the usefulness of such programs as consultants in patient care.

Mechanisms of active transport; biochemical kinetics: B. Bunow (LAS); J. Rinzel (NIAMDD); J. De Simone et al. (Medical College of Virginia): experimental and mathematical studies of the energy mechanisms for active transport, and of multi-state biochemical kinetics in cells and membranes.

General mathematical and computational methods: E. Hill (LAS);
R. Shrager (LSMM): Study of methods of fitting non-linear models
utilizing other than least squares criteria. Evaluating methods
of organizing large data files for rapid storage and retrieval.

Computer aided analysis of electrocardiograms: J. Bailey, M. Horton
(LAS): Separate studies, conducted in collaboration with the
Cardiology Branch, NHLBI, and a cardiologist in Glasgow, Scotland,
to evaluate the utility of leading computer programs for ECG
interpretation. Both studies include clinical documentation.

Computer-based modeling of pulmonary gas exchange: Many LAS staff
members; staff of Diagnostic Imaging, (CC), and Pulmonary laboratory
(NHLBI). (See Highlights, Project No. 3)

Computer systems for diagnostic imaging: J. Bailey, M. Douglas,
B. Line (LAS); H. Ostrow (CSL); M. Green and others (Diagnostic
Imaging, CC): Development and application of computer systems
(see Highlights, Project No. 2) to such diagnostic imaging activities
as ECG-gated radionuclide angiocardiography, functional mapping and
other scintigraphic studies of kidney, brain, heart and lung.

Hybrid computing to analyze physiologic signals and construct
simulation models: E. Pottala, R. Covacci (LAS), S. Vallerga
(Lab. Neurophys., NINCDS): Using LAS minicomputer system (MAC-16)
for hardware simulation of physiologic functions (e.g., retinal
cell activity) and analysis of analog signals (myogram,
ultrasonogram, etc.)

Statistical research in clinical pathology: E. Harris (LAS),
G. Shakarji (DMB); clinical chemists in California, U.K.:
Application of variance component and time series analysis to
description of reference distributions of clinical laboratory
tests, to serial studies of normal biochemistries, and to the
design of criteria for recommended precision and accuracy of
analytic methods.

III. Publications

1. Agress, H., Jr., Bacharach, S.L., Hammock, M.K., Green, M.V.,
    Johnston, G.S. and Di Chiro, G.: Stochastic analysis of
    133-Xe clearance for determining regional cerebral blood
    flow in a primate model. Stroke 8: 222-226, 1977.

2. Agress, H., Jr., Levenson, S.M., Gelfand, M.J., Johnston, G.S. and Bailey, J.J.: Functional mapping and related computer-generated images in radionuclide renography. Applied Radiology 5: 202-208, 1976.

3. Bacharach, S.L., Green, M.V., Borer, J.S., Line, B.R., Bradley-Moore, P.R., Ostrow, H.G. and Johnston, G.S.: Real-time collection, analysis, and display of nuclear medicine data. Proceedings of the Seventh Symposium on Sharing Computer Programs and Technology in Nuclear Medicine. Society for Nuclear Medicine, 475 Park Avenue South, New York, N.Y., 10016, 1977 (in press).

4. Bailey, J.J., Horton, M.R. and Itscoitz, S.B.: The importance of reproducibility testing of computer programs for electrocardiographic interpretation: Application to the automatic vectorcardiographic analysis program (AVA 3.4). Comp. and Biomed. Res. 9: 301, August 1976.

5. Bailey, J.J. and Horton, M.R.: Advantages of automation of ECG analysis with conventional (heuristic) criteria. Trends in Computer-Processed Electrocardiograms. Edited by J.H. van Bemmel and J.L. Willems. North Holland Publishing Company, New York, 1977, pages 221-228.

6. Bradley-Moore, P.R., Klickna, J., Line, B.R., Jones, A.E. and Johnston, G.S.: A nuclear medicine reporting system-renal. Proceedings of the Seventh Symposium Sharing Computer Programs and Technology in Nuclear Medicine. Society for Nuclear Medicine, 475 Park Avenue South, New York, N.Y., 10016, 1977 (in press).

7. Bunow, B. and Caplan, S.R.: Chemical Reactions and Membranes. Biophysics of Membrane Transport, Part I, 9-30, Agricultural Univ. of Wroclaw, 1976.

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10. Dubois, A., Van Eerdewegh, P., Line, B.R., Van Maele, P. and Gardner, J.D.: A new method for simultaneous determination of gastric emptying and secretion. Proceedings of the Fifth International Symposium on Gastrointestinal Motility. Editor: G. van Trappen. Typeoff Press, Herrenthals, Belgium, 1976, pages 244-247.

11. Dunham, R.G., Line, B.R. and Johnston, G.S.: A comprehensive software system for producing functional maps. Proceedings of the Seventh Symposium Sharing Computer Programs and Technology in Nuclear Medicine. Society for Nuclear Medicine, 475 Park Avenue South, New York, N.Y., 10016, 1977 (in press).

12. Fletcher, J.E.: Some model results on hemoglobin kinetics and its relationship to oxygen transport to blood. Oxygen Transport to Tissue-II, edited by J. Grote, D. Reneau, and G. Thews, Plenum Press, New York, 1976, Vol. 75, 251-259.

13. Fletcher, J.E. and Spector, A.A.: Alternative models for the analysis of drug-protein binding. Molecular Pharmacology, Vol. 13, 387-399, May 1977.

14. Fletcher, J.E.: A generalized approach to equilibrium models. Jour. of Physical Chemistry (in press).

15. Green, M.V., Bacharach, S.L., Douglas, M.A., Line, B.R., Ostrow, H.G., Redwood, D.R., Bailey, J.J. and Johnston, G.S.: The measurement of abnormalities with high temporal resolution ECG-gated scintigraphic angiocardiography. IEEE Transactions on Nuclear Science. Vol. NS-23 (3): 1257-1263, 1976.

16. Green, M.V., Bailey, J.J. Ostrow, H.G., Douglas, M.A., Pearlman, A.S., Brody, Itscoitz, S.B., Redwood, D.R. and Johnston, G.S.: Computerized EKG-gated radionuclide angio-cardiography: a non-invasive method for determining left ventricular volumes and focal myocardial dyskinesia. Computers in Cardiology. IEEE Catalog No.75CH1018-16. IEEE Computer Society, Long Beach, CA., 90803, 1975, pp. 137-141.

17. Harris, E.K.: Some theory of reference values. II. Comparison of some statistical models of intra-individual variation in blood constituents. Clin. Chem., 22, 1343-1350 (August, 1976).

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19. Kernevez, J.P., Bunow, B., Duban, V.C., Joly, G. and Thomas, D. Structuration en Espace Spontanee a l'Interieur d'une Membrane Mono-Enzymatique. C.R. Acad. Sci. Paris 284A, 195-198, 1976.

20. Kushner, T.R., Line, B.R., Bacharach, S.L. and Johnston, G.S.:
    A spirometric method for gating xenon ventilation studies.
    Proceedings of the Seventh Symposium Sharing Computer Programs
    and Technology in Nuclear Medicine. Society for Nuclear Medicine,
    475 Park Avenue South, New York, N.Y., 10016, 1977 (in press).

21. Line, B.R.: A command processing system for the analysis of
    scintigraphic data. The Fifth International Conference on
    Information Processing in Medical Imaging, Edited by the
    Commission for Atomic Energy, ISBN-2-7272-0005-6, Orsay, France,
    1977 (in press).

22. Line, B.R. Dayhoff, R.E and Bailey, J.J.: An algorithm for the
    production of regional gas partial pressures and blood contents
    from scintigraphic and physiologic data using an alveolar gas
    exchange model. Proceedings of the Seventh Symposium on
    the Seventh Symposium on Sharing Computer Programs and Technology
    in Nuclear Medicine. Society for Nuclear Medicine, 475 Park
    Avenue South, New York, N. Y., 10016, 1977 (in press).

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    Bailey, J.J.: An algorithm for the selection of lung margins
    in scintigraphic ventilation-perfusion studies. Proceedings of
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    Intra-individual variation of some serum constituents and its
    relevance to population-based reference ranges. Clin. Chem.
    23, 842-850 (May 1977).

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    of the 30th ACEMB, 1977 (in press).

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    protein binding. Nutrition and Drug Interrelationships,
    Academic Press (in press).

27. Spector, A.A. and Fletcher, J.E.: Transport of fatty acid in
    the circulation. The Physiology of Lipids and Lipoproteins in
    Health and in Disease. Editors J.M. Dietschy, J.A. Dietschy,
    J. A. Ontko and A.M. Gotto, American Physiological Society
    (in press).

28. Williams, G.Z., Harris, E.K. and Widdowson, G.M.: Comparison of estimates of long-term analytical variation derived from subject samples and control serum. Clin. Chem. 23, 100–104 (January 1977).

29. Wright, G. Wasserman, D., Pottala, E.W. and Dakes-Dubos, F.: The effect of general fatigue on isometric stress-endurance measurements and the electromyogram of the bicep brachii. American Industrial Hygiene Association Journal 37: 274–279, 1976.

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Computer Aided Analysis of Electrocardiograms

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J.J. Bailey   Head, Med. Appl. Sec.   LAS   DCRT
M.R. Horton   Computer Systems Analyst   LAS   DCRT
J. Gottdiener   Chief, ECG Laboratory   CB   NHLBI
D.D. Savage   Clinical Associate.   CB   NHLBI

COOPERATING UNITS (if any)

P. Lawrence, Cardiology Dept, Walter Reed Army Medical Center
P. MacFarlane, Medical Cardiology, Glasgow Royal Infirmary, Scotl;

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Medical Applications Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, Maryland   20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	1.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

These studies continuing since 1970 have been directed toward the evaluation of accuracy, clinical utility, and cost effectiveness of various computer systems for analysis of routine electrocardiograms (ECG's).

Background and Objectives:

In the past fifteen years numerous computer programs implemented upon a variety of computer systems have been developed for analysis of routine ECG s. Computer processing of ECG s has become a sizeable enterprise in many parts of the country, including both commercial bureaus offering service for a fee and non-commercial (academic or government) centers establishing the capability for themselves.

Since 1970, LAS in collaboration with CB, NHLBI has studied various programs to determine which, if any, would be useful to implement on the NIH campus. As a result of this work, an evaluation methodology was evolved which was published in 1974 and has become one of the standard references in the field. Although a program was selected and implemented in 1974 for daily use at NIH, additional programs and other computer systems continue to be evaluated as possible improvements in the NIH system with regard to cost and accuracy. Past evaluations have included the ECAN-D program (1964), the Mayo-IBM program (1968), the experimental IBM program (1971), the AVA 3.4 (Pipberger) program(1975), and the ECAN-E program (1975) (ref. 1 and 2).

In an attempt to evaluate sensitivity and specificity of criteria used by programs, a group of 300 cases was collected in FY 76 for which documentation of the patient's status was sought in cardiac catheter studies in the Cardiology Branch, NHLBI. This project was terminated when the chief collaborator in the cardiac laboratory left NIH. However, some of these cases also had echocardiography studies and are part of a group described below.

Progress during FY 77:

A series of 300 ECGs were collected on patients in the Glasgow Royal Infirmary, (GRI), Scotland. Clinical documentation of the patients' cardiovascular status by non-ECG means in the form of enzyme studies, cardiac catheter laboratory data, etc., was obtained whenever such investigations were warranted, i.e., in most cases. The standard 12 lead ECG data was analyzed by the IBM progran at NIH; modified McFee lead (XYZ) ECG data was analyzed by a program developed at GRI. The results of these two programs are being compared with respect to accuracy where clinical documentation exists and with respect to cardiologist agreement in all other cases. A manuscript is being prepared.

A series of 110 ECG s were collected by CB, NHLBI on patients with a variety of conditions including hypertension, valvular disease, and coronary disease. In all cases, the size of the left ventricle has been estimated from ultrasound measurements of the septal wall thickness, posterior wall thickness, and internal end-diastolic diameter. The IBM program uses ECG features to compute points towards a diagnosis of left ventricular hypertrophy (LVH) in a manner somewhat similar to the

Romhilt-Estes point score. The AVA3.4 (Pipberger) program uses Frank lead (XYZ) ECG features to compute probabilities for LVH. The correlation of these two computerized LVH algorithms with the ultrasound measurements will be the subject of another manuscript.

Medical corpsmen at Walter Reed Army Medical Center are being trained to read ECG s by an Army cardiologist. When their training is complete, they will be matched against the IBM program (1974) on a set of cases which have already been classified by three independent cardiologists at NIH. This study is directed to questions such as comparative accuracies and costs of the corpsman reader versus the computer programs when performing as pre-processors to the over-reading cardiologist.

Significance:

The estimated number of computer-processed ECGs in North America in 1971 was 600,000; in 1972, it was one million; and in 1974 it was 4 million. In view of this exponential increase in computer usage, it will become ever more important to have methodologies and guidelines by which ECG computer systems can be evaluated.

These studies seek to establish the diagnostic limits of ECG itself and the degree to which computerized algorithms may achieve these limits. Important evaluation methodology continues to be developed, which may have a significant impact on the further diffusion of computer technology in electrocardiography.

Proposed Course:

The testing of these programs with clinically documented data, i.e., cases with correlative data from cardiac catheter laboratory studies, echocardiography, or scintigraphic studies, is expected to be completed within FY79.

Publications and Abstracts:

1. Bailey, J.J., Horton, M.R. , Itscoltz S.B.: The importance of reproducibility testing of computer programs for electrocardiographic intrepretation: Application to the automatic vectorcardiographic analysis program (AVA 3.4) Comp. and Biomed. Res. 9:301, August, 1976.

2. Bailey, J.J., Horton, M.R.: Advantages of automation of ECG analysis with conventional (heuristic) criteria. Trends in Computer-processed Electrocardiograms in 98. Edited by J.H. van Bemmel and J.L. Willems. North Holland Publishing Company, New York, 1977, pages 221-228.

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Computer Systems for Diagnostic Imaging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Bailey	Head, Med Appl. Sec	LAS	DCRT
	M.V. Green	Ch, Appl. Phisics Sec	DI	CC
	B.R. Line	Senior Asst Surgeon	LAS	DCRT
OTHER:	M.A. Douglas	Computer Systems Analyst	LAS	DCRT
	M.R. Horton	Computer Systems Analyst	LAS	DCRT
	E.W. Pottala	Engineer	LAS	DCRT
	S.L. Bacharach	Physicist	DI	CC
	C.L. Blei	Staff radiologist	DI	CC
	P.R. Bradley-Moore	Staff Fellow	DI	CC
	R.G. Dunham	Computer Specialist	DI	CC
	G.S. Johnston	Ch, Diag. Imaging Br.		CC
	A.G. Ostrow	Engineer	CSL	DCRT

COOPERATING UNITS (if any)

Diagnostic Imaging Department, CC, NIH
Computer Systems Laboratory, DCRT, NIH

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Medical Applications Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, Md.

TOTAL MANYEARS: 3.1	PROFESSIONAL: 3.0	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves the computer-based mathematical analysis, pattern recognition, and image processing in support of diagnostic activities in the Diagnostic Imaging Department of the Clinical Center and collaborating Institutes. Applications include computerized ECG-gated radionuclide angiocardiography, scintigraphic studies of regional cerebral blood flow, scintigraphic studies of gastric fluid dynamics, pulmonary ventilation-perfusion scintigraphs, and computer analysis of ultrasonograms.

PHS-6040

Background and Objectives:

Since FY72 LAS with engineering support from CSL, DCRT and in collaboration with the Diagnostic Imaging Department, CC, has accomplished acquisition of minicomputer hardware and the development of software necessary to process data from three scintillation cameras in the Diagnostic Imaging Department.

The objective of this program is continuing development of computer-based algorithms which have already found wide-ranging applications, including: fitting mathematical models; mapping the parameters of such models over time and in different regions of an organ; image restoration by deconvolution and non-restorative image enhancement; interpolation, expansion, and contraction of image arrays. Application to other noninvasive imaging systems such as ultrasonograms, and the incorporation of other physiologic signals with the imaging studies (e.g. ECG-gated heart studies) are also under investigation.

Progress during FY77:

During FY76-77 the development of the extended nuclear utility (ENU) was completed and documented (ref. 12). ENU allows the rapid modular construction of complex processing programs using newly developed program modules as well as modules from a library of already developed algorithms. One important offshoot from ENU is a system for real time collection, analysis, and display of scintillation data (ref. 3). This system is important for the clinical investigator who wishes to do repeated studies of organ function before and after therapeutic intervention (e.g. radionuclide angiocardiography, pulmonary scintigraphy).

Another important derivative of ENU is a collection of programs to map dynamic, time-dependent parameters into a single image (ref. 6). A typical application of such mapping programs was the determination of regional cerebral blood flow in monkeys, before, during, and after experimentally induced infarction (ref. 1). Another such application was in the determination of gastric fluid dynamics (ref. 7). These programs have also been used in dynamic studies of heart, lung, and kidneys as described below.

A functional map, which is a single image containing the regional distribution of dynamic, time-dependent parameters of a given organ, is a useful tool for investigating renal physiology. Through FY76, this method has been applied to 130 patients and found to enhance the detection of functional abnormalities in more than one-third of the cases (ref.2). In one case the functional maps showed slight residual impairment of function in the left kidney 18 months after removal of a

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renal stone and relief of obstruction. The routine scintigraphic studies (without computer processing) were interpreted as normal. In another case, the functional maps showed a normal uptake of isotope over the corticomedullary areas but a delayed uptake over the pelvic region of the left kidney. The functional maps also showed a delayed washout of isotope from a wedge-like corticomedullary area in the mid and lower pole of the kidney but the washout from the pelvis was normal. These results meant that there was an intrarenal obstruction in the wedge-like area and that there was no extrarenal obstruction (e.g. a blocked ureter). This interpretation could not be made from the routine scintigraphic study which was read as compatible with extrarenal obstruction. The functional maps are now part of a routine radionuclide renography (ref. 4).

An important clinical application, which has been the subject of investigation since FY74, concerns computer-based ECG-gated radionuclide angiocardiography (refs. 8 and 9). This method originally required framing and processing on a large scale digital computer (PDP-10). In FY76-77 it was reprogrammed to run in real time on the LAS minicomputer system in the Diagnostic Imaging Department, thus enabling studies during both rest and exercise on patients with suspected coronary disease (ref. 3).

Use of a computer-based method for scanning the status of ventilation and perfusion in the lungs began in FY73. At that time it proved useful in following the changes in pulmonary dynamics in patients who underwent surgical repair of valvular heart disease. In FY76-77 this method was refined by the incorporation of volume gating and by automatic edge detection (refs. 10 and 11). Also in FY76-77 the results of pulmonary scintigraphy have been applied to over 300 patients, 100 of them with idiopathic pulmonary fibrosis (ref. 5).

In FY76 a package of image processing routines (IMAGE) was developed on the PDP 10 System. This package is capable of several functions: e.g., edge detection, spatial derivatives, iterative deconvolution, noise detection and application of selective filters. Currently it is being used to design an algorithm for automatic detection of the left ventricle in radionuclide angiocardiography. When this algorithm is perfected, it will be implemented on the LAS minicomputer system (HP 5407) in the Diagnostic Imaging Department and used routinely; it will greatly reduce the human intervention and time now needed in these studies.

The Diagnostic Imaging Branch has purchased an ultrasound imaging device (Picker). This device emits data in the mega Hz. range whereas the LAS minicomputers (HP 5407) can accept only a kHz data rate. A set of projects awaits the interfacing of a hardware buffer device (Biomation) to both the ultrasound and the minicomputer which will accept the ultrasound data at a mega Hz. rate and deliver the data to the mini- computer at a kHz. rate.

Significance:

Scintigraphy is a noninvasive tool which shows considerable detail concerning the dynamic function of an organ on a regional basis. Computer processing not only enhances scintillation images but allows quantification of the dynamic function. Real time implementation of algorithms on the minicomputers allows the clinical investigator to perform repeated studies on patients with exercise or therapeutic manipulation, thus better elucidating the nature of the patient's pathophysiology.

Ultrasonography is a diagnostic imaging tool with wide application. Image enhancement and automatic pattern recognition should greatly improve its clinical utility.

Proposed Course:

NHLBI has purchased its own minicomputer system for routine radionuclide angiography studies. This means that more time will be available for development on the LAS minicomputers in the Diagnostic Imaging Department.

The pulmonary scintigraphic data combined with analysis of ventilatory dynamics and blood gases will provide the basis for an extensive program in the mathematical modeling of pulmonary pathophysiology.

Validation studies of functional mapping of radionuclide renography utilizing animals are currently being carried out by a clinician (staff fellow) in NM CC. These studies involve experimentally induced lesions such as, arterial constriction, ureteral obstructions, hematoma, toxic nephritis, etc. Data from a few lupus nephritis patients have also been obtained. When validated by animal studies, this noninvasive diagnostic method should greatly improve the evaluation of disease state and response to therapy in patients with lupus nephritis (NIAMDD), renal hypertension (NHLBI), and neoplasis affecting the kidneys and urinary tract (NCI).

Clinicians in the Diagnostic Imaging Department propose to study breast masses by computer-processed ultrasonograms. If successful, this method would be very useful since it does not subject the patient to the risk of radiation exposure.

Publications and Abstracts:

1. Agress, H.Jr., Bacharach S.L., Hammock M.K., Green M.V., Johnston, G.S., Di Chiro G.: Stochastic analysis of 133-Xe clearance for determining regional cerebral blood flow in a primate model. Stroke 8: 222-226, March 1977.

2. Agress, H. Jr., Levenson S.M., Gelfand M.J., Johnston G.S.,
    Bailey, J.J. Functional mapping and related computer-generated
    images in radionuclide renography. Applied Radiology, 5:202-208,
    Nov.-Oct., 1976

3. Bacharach S.L., Green, M.V., Borer, J.S., Line, B.R.,
    Bradley-Moore, P.R., Ostrow, H.G., Johnston, G.S.: Real-time
    collection, analysis, and display of nuclear medicine data.
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    and Technology in Nuclear Medicine. Society for Nuclear Medicine,
    475 Park Avenue South, New York, N.Y., 10016, 1977 (in press).

4. Bradley-Moore, P.R., Klickna, J., Line, B.R., Jones, A.E.,
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    Proceedings of the Seventh Symposium Sharing Computer Programs and
    Technology in Nuclear Medicine. Society for Nuclear Medicine, 475
    Park Avenue South, New York, N.Y., 10016, 1977 (in press).

5. Crystal, R.G., Fulmer, J.D., Roberts, W.C., Moss, M.L., Line,
    B.R., Reynolds, H.Y.: Idiopathic pulmonary fibrosis: Clinical,
    histologic, radiographic, physiologic, scintigraphic, cytologic,
    and biochemical aspects. Ann. Int. Med. 85: 769-788, 1976.

6. Dunham, R.G., Line, B.R., Johnston, G.S.: A comprehensive
    software producing functional maps. Proceedings of the Seventh
    Symposium Sharing Computer Programs and Technology in Nuclear
    Medicine. Society for Nuclear Medicine, 475 Park Avenue South, New
    York, N.Y., 10016, 1977 (in press).

7. Dubois, A., Van Eerdewegh, P., Line, B.R., Van Maele. P.,
    Gardner, J.D.: A new method for simultaneous determination of
    gastric emptying and secretion. Proceedings of the Fifth
    International Symposium on Gastrointestinal Motility. Editor: G.
    van Trappen. Typeoff Press, Herrenthals, Belgium, 1976, pages
    244-247.

8. Green, M.V., Bacharach, S.L., Douglas, M.A., Line, B.R.,
    Ostrow, H.G., Redwood, D.R., Bailey, J.J., Johnston G.S.: The
    measurement of abnormalities with high temporal resolution
    ECG-gated scintigraphic angiocardiography. IEEE Transactions on
    Nuclear Science. Vol. NS-23 (3): 1257-1263,
    1976.

9. Green, M.V., Bailey, J.J., Ostrow, H.G., Douglas, M.A.,
    Pearlman, A.S., Brody, W.R., Itscoitz, S.B., Redwood D.R., Johnston
    G.S.: Computerized EKG-gated radionuclide angiocardiography: a
    non-invasive method for determining left ventricular volumes and
    focal myocardial dyskinesia. Computers in Cardiology. IEEE
    catalog No. 75CH1018-16. IEEE Computer Society, Long Beach, CA.,
    90803, 1975, pp. 137-141.

10. Kushner, T.R., Line, B.R., Bacharach, S.L., Johnston, G.S.: A spirometric method for gating xenon ventilation studies. Proceedings of the Seventh Symposium Sharing Computer Programs and Technology in Nuclear Medicine. Society for Nuclear Medicine, 475 Park Avenue South, New York, N.Y., 10016, 1977 (in press).

11. Line, B.R., Jones, A.E., Johnston, G.S., Crystal, R.G., Bailey, J.J.: An algorithm for the selection of lung margins in scintigraphic ventilation-perfusion studies. Proceedings of the Sixth Symposium for the Sharing of Computer Programs and Technology in Nuclear Medicine. Society For Nuclear Medicine, 475 Park Avenue South, New York, N.Y., 10016, 1976, pages 52-59.

12. Line, B.R.: A command processing system for the analysis of scintigraphic data. The Fifth International Conference on Information Processing in Medical Imaging, Edited by the Commission for Atomic Energy, ISBN-2-7272-0005-6, Orsay, France, 1977 (in press).

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Investigation of Hybrid Computing for the Construction of Simulation Models and for the Analysis of Physiologic Signals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: E.W. Pottala   Elec. Engineer   LAS   DCRT

OTHER: J.J. Bailey   Head Medical Applications   LAS   DCRT
                              Section
        M.R. Horton   Computers Systems Analyst   LAS   DCRT
        R. Covacci   Visiting Scientist   LAS   DCRT
        S. Vallerga   Visiting Scientist   LNP   NINCDS

COOPERATING UNITS (if any)

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LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT,NIH, Bethesda, Maryland   20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.9	1.8	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project was undertaken to develop physiologic simulation models using hybrid computing and also to use hybrid computing techniques to analyze physiologic signals such as electrocardiogram, electroencephalogram, ultrasonogram, and scintigram.

Background and Objectives:

In some simulation models, certain pieces or functions can be split off and implemented in hardware circuitry or a set of microprocessors. This has several advantages. First, parallel processing is allowed, which can shorten computing time and make interactive model testing feasible. Second, the hardware circuitry or microprocessors are usually quite inexpensive. And third, some models are so complicated and extensive, that their implementation on a large scale digital computer is not feasible; whereas with hybrid computing, such models may be readily achieved. An example was the model of the Purkinje network in the alligator cerebellum which required a system of 35 cells connected by nonlinear differential equations (completed in FY 76).

Since FY72 the LAS Laboratory minicomputer system (MAC 16) has been developed and utilized for various projects including (1) the construction of physiologic simulation models and (2) the processing of physiologic signals. Since FY72 the system has been interfaced with the Marquette tape drive (for routine ECG s from the clinical Center); with the Honeywell 7600 analog tape transport; with a general purpose switch-filter network; with a real time spectral analyzer and ensemble averager; and with a neural control panel for simulation of neural networks (FY75) and central nervous system subsystems (cerebellum, FY76).

A general advantage of this system is that an investigator can automatically pre-process (edit, filter, and digitize) dynamic physiologic data so that optimal use of a large scale digital computer can be obtained. This was demonstrated in electromyograms from subjects on a muscle fatigue protocol studied by the National Institute of Occupational Safety and Health (ref. 2). This facility was also used for electrocardiogram (ECG) and ventricular pressure data in monkeys (FY76) and also ECG data from Glasgow Royal Infirmary (see ECG section).

Progress during FY77:

The Laboratory of Neurophysiology, NINCDS, is studying the electrophysiology in the retina of the larvae tiger salmander. The Baylor-Hodgkin-Lamb model of a cone cell requires six compartments connected by six linear differential equations and three compartments involving sodium and potassium fluxes related by three nonlinear differential equations. This model has been implemented in hardware by LAS (ref. 1). It was also implemented in software on the PDP-10 so that the hardware model could be thoroughly checked out. The model parameters were adjusted to best fit the actual photoresponses (membrane potential) recorded intracellularly from cones in the retina of the larva tiger salamander. Stimuli consisted of flashes and steps of light. The responses of the model and the real cone cell were in good agreement for 10 millisecond flashes and 0.7 second steps of light whose

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intensities ranged over 2.5 log units with the intensity of the
unattenuated light at 1.5 X 10**17 photons per second per square
centimeter.

The LAS minicomputer system is being upgraded by the incorporation
of a Macro-Arithmetic Processor (MAP). This hardware device can process
large arrays very rapidly; for example, a Fast Fourier Transformation of
1024 data points can be produced in 20 milliseconds. The array
processing capability will enable interactive design of filtering
algorithms for many different physiologic signals and also the
implementation of such filtering algorithms in real time.

Proposed Course:

Currently LAS is building a hybrid modeling system for retinal
physiology consisting of hardware models of cone cells, rod cells,
horizontal cells, and bipolar cells connected together in a network and
driven by the LAS minicomputer system. This hybrid modeling system
should permit a rapid test of all possible synaptic configurations to
determine the one which best fits observed photoresponses and eventually
the designing of the proper electro-physiological experiments to verify
it.

The installation of the MAP will allow extensive studies into use
of orthogonal transforms and other tools for filtering of physiologic
signals and image enhancement algorithms for ultrasonographic and
scintigraphic data.

This LAS minicomputer system will be used to compute dynamic lung
compliance on patients in the Pulmonary Branch (see pulmonary
pathophysiology section).

Publications and Abstracts:

1. Pottala, E.W., Covacci, R., Colburn, T.R., Vallerga, A.: Hardware model
   of a tiger salamander cone cell, Proceedings of the 30th ACEMB, 1977
   (in press).

2. Wright G., Wasserman D., Pottala, E.W., Dakes-Dubos, F.: The effect of
   general fatigue on isometric stress-endurance measurements and the
   electromyogram of the bicep brachii. American Industrial Hygiene
   Association Journal 37: 274-279, 1976.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER
		..Z01 CT 0005-07 LAS

PERIOD COVERED
July 1 1976 to September 30 1977

TITLE OF PROJECT (80 characters or less)
Mathematical Modeling of Biological Processes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.E. Fletcher	Head, Applied Mathematics Section	LAS DCRT
OTHER:	M. Bieterman	Mathematician, AMS	LAS DCRT
	A. Spector	Professor, Univ. of Iowa Med. School	
	R. Lutz	Chemical Engineer, BEIB	DRS

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project consist of three areas of investigation: (1) Mathematical Models of Binding Equilibria, (2) Mathematical Modeling of Substrate Transport in the Microcirculation, and (3) Numerical Methods for the Solution of Transport and Diffusion Processes in Biomedicine.

All areas have in common the theoretical development of conceptual models as mathematical formulations from basic physical, biochemical or biomedical principles. Methods for solution via computer are studied and satisfactory methods are used to produce unknown parameters from experimental data, simulate laboratory experiments, and/or to validate experimentally determined ranges of variation in biomedical phenomena.

This new project is an outgrowth of a contractual effort reported under ZOl CT 00005-06 LAS during FY 76.

Background and Objectives:

The objective of this project is to investigate the use of simulation programs in physiology as diagnostic and patient management aids to physicians and other clinical staff. The previous contract effort, completed in FY 77 by the George Washington University, has revealed that many such programs now in limited use are deficient in their physiologic description of interdependent metabolic pathways. One such deficiency, concerning acid-base balance, is now being considered in detail by this laboratory.

Significance to Biomedical Research:

Such simulations offer the clinician the opportunity to try a proposed course of treatment on an ideal (computer) patient, without the attendant risk of damage to the actual patient.

Progress in FY 77:

The contract effort developed a performance framework in which such programs could be evaluated, and possible weaknesses identified. Current laboratory efforts involve the implementation and evaluation of existing programs not considered under this contract, and the feasibility of their use in a clinical environment. As such programs become operational, efforts will be made to evaluate their utility in a clinical environment.

Proposed Course:

Pending the outcome of feasibility studies and manpower availability, future efforts will consider the development of physiologic simulators with correct descriptions of interdependent pathways. Implementation of these programs in a variety of clinical settings will follow the developmental stage. One possibility, requiring the cooperation of the Clinical Pathology Department (CC), would be to test an acid-base balance program with existing data on electrolyte, blood gas, and pH measurements on patients before and after specific therapeutic intervention.

Publications and Reports:

Contractor's final report: Evaluation of cardiovascular-renal computer simulations (August, 1977). C.S. Tidball project director, G.W.U.

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)
General Mathematical and Computational Collaborative Efforts

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: E. Hill   Computer Scientist   LAS DCRT

OTHER: R. Shrager   Mathematician   LSMM DCRT
        A. Meltzer   Professor, G.W. Univ

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland   20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project was completed in FY 77. A curve fitting methodology utilizing the Levenberg-Marquardt method for fitting non-linear models was extended to norms other than L_2 (least squares). Heuristics are proposed and programs have been developed which offer these methods as practical tools. Publications describing these methods have been submitted for publication.

A second project area involved a comparison of methods for organizing very large amounts of stored data which facilitate rapid storage and retrieval. Existing hashing methods were evaluated and new algorithms are proposed for very large data bases. A methodology for evaluation and comparison of schemes is described.

Objectives:

This project is concerned with the development of two areas
of computers and mathematics in the biosciences.

Background:

The first area is concerned with Nonlinear Model Fitting and
Parameter Estimation. The "standard" methods of least squares have
been extensively developed for fitting nonlinear models to
experimentally obtained data, with the estimation of unknown parameters,
in these models as an objective. For many applications, the least
squares criteria is not appropriate and may introduce unnecessary
computational difficulties. For example, the fitting of data taken
over a wide range of measurements and fitted without weights tends to
bias the results toward the data with larger independent variables.
The problems of ill-conditioning with systems having several parameters
is also well known. Until recently, methods for fitting models with
nonlinear parameters were not available in other than the least squares
methods. The first part of this project is concerned with such methods.

Progress in FY 77:

In FY 76 and 77 the Levenberg-Marquardt method concepts for model
fitting in the least squares norm were extended to nonlinear models for
fitting in the L_1 norm, $(L_1 = \min \Sigma \mid \bar{y} - \hat{y} \mid_i)$ and L_∞ norm,
$[L_\infty = \min(\max_{1 \leq i \leq m} \mid \bar{y} - \hat{y} \mid_i)]$. Computer algorithms using these
concepts have been developed and implemented in the PL/I Language on
the IBM 370/168 system. Technical reports and articles describing
these methods have been submitted for publication.

Proposed Course:

Additional efforts in this area, subject to limitations of
manpower and funding will examine mathematical and statistical models
compatible to the L_1 and L_∞ fitting norms and the development of
error estimates for the derived parameters.

Significance to Biomedical Research:

The determination of unknown parameters in mathematical and
statistical models is a central task of biomedical data analysis. Data
ranging from demographic information to electron spin measurements are
analyzed by the fitting of models to experimental or observed data.
Improvements in, or alternative procedures to, present fitting methods
clearly are of benefit to all such analyses.

Background and Objectives:

A second project area involves a comparison of methods for organizing large amounts of stored data on direct access storage devices to facilitate fast retrieval of the desired information. This project was undertaken in order to classify as to performance the various retrieval methods and their associated data structures.

In a very large data base involving retrieval and updating, the major factor of immediate concern is the average number of accesses to the direct access storage device to complete a request. The average number of accesses to store and retrieve items on a direct access storage device for hashing methods and other techniques were considered.

Significance to Biomedical Research:

Such methodology has application to the design of storage and retrieval schemes for medical records, computer-aided diagnoses, medical linguistics, and other technical areas requiring search and retrieval in very large data or decision files.

Progress in FY 77:

A new algorithm and performance measures for chaining with coalescing lists were constructed, and new performance measures were found for storing and retrieving with a binary search tree and a tree stored on a direct access storage device. Algorithms were constructed to perform retrieval, insertion, deletion and the inverted file generation operations for an inverted file. New performance measures have been developed for an inverted file. The methods are developed using a component concept. A hybrid method involving components is used for the linked files. All methods were analyzed, along with their data structures, to show their effect on the average number accesses to the direct access storage device while processing a request. Finally, a comparison criterion was developed and each method was compared. The results of this study have been documented in report form, and a number of papers have been submitted for publication.

Proposed Course:

Further efforts in this area will concentrate on applications of new algorithms to specific biomedical applications. Due to higher priority utilization of manpower, progress in FY 78 is expected to be limited.

Publications:

1. Shrager, R. and Hill, E.:   Curve-Fitting in the L_1 and L_∞ Norm (abstract, poster presentation), SIAM Annual Meeting, June 13, 1977.

2. Shrager, R. and Hill, E.: Curve-Fitting in the L_1 and L_∞ Norms, SIAM Journal Numerical Analysis, 1976, (Submitted).

3. Hill, E. and Shrager, R.: Curve-Fitting in the L_1 and L_∞ Norms Using Stiefel's Algorithm, Transactions on Mathematical Software, 1976, Submitted.

4. Hill, E.: Curve-Fitting in the L_1 and L_∞ Norms Using the Simplex Method, Transactions On Mathematical Software, 1976, Submitted.

5. Hill, E.: A Comparison of Very Large Data Bases, <u>Proceedings of the Third International Conference on Very Large Data Bases</u>, Tokyo, Japan, October, 1977.

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Statistical Research in Clinical Pathology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: E. K. Harris   Chief, Lab. of Applied Studies   LAS DCRT

OTHER: G. Shakarji   Supv. Systems Analyst   DMB DCRT
         G. Z. Williams   Director, Institute for Health
                                 Research, San Francisco, Ca.
         S. S. Brown   Clinical Chemistry Service
                                 Clinical Research Centre
                                 Harrow, England

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Applied Studies

SECTION

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In cooperation with Dr. G. Z. Williams and staff, records of some 30 different biochemical and hematological tests performed serially on several hundred healthy volunteers are being collated to provide a large-scale test of the usefulness of each of 3 stochastic forecasting models described in last year's report. These models together with the general theory of variance components in clinical chemistry, have also been applied to the development of criteria for setting goals of precision and accuracy in laboratory methods, depending on the context of use. Analysis of a 5-month study of weekly serum biochemistries in 37 normal volunteers has been completed and published, providing new data on intra-and-inter-individual biological variances. Further work is in progress, utilizing these data, to construct and test theoretical links between population-based reference distributions and individual series of results so as to improve the forecasting accuracy of statistical time series models applied to short series.

Objectives:

To investigate the application of statistical theory, particularly the use of variance components and the theory of discrete time series, to the interpretation of clinical laboratory measurements and the evaluation of analytic methods.

Background and Progress during FY 77:

Last year saw the development of several appropriate stochastic models and their application to short time series of cholesterol measurements collected from a small group of healthy individuals in the monitoring program directed by G. Z. Williams of the Health Research Institute, San Francisco (Ref. 1). During the present year, data have been collated on several hundred healthy individuals in this program in whom some 30 different biochemical and hematological analytes have been measured on at least 4 repeated occasions, 8-12 months apart. Computer tapes of these data are currently being processed through statistical packages developed at DCRT to execute components of variance analysis and estimation of parameters, as a preliminary step to identification of the appropriate stochastic model describing each subject-constituent series.

On invitation of the College of American Pathologists, these stochastic models together with basic concepts of physiological and analytic variances were applied to a quite different purpose, the development of statistical principles to guide decisions concerning proper levels of precision and accuracy in laboratory methods(Ref. 2). Defining several common contexts in which clinical laboratory tests are required, an appropriate statistical model was constructed for each context, involving those components of variance specific to that context. For example, in a population screening survey, the predictive value of a laboratory test necessarily involves inter- as well and intra-individual variance. Other decision situations concern only a single patient, either in terms of an immediate diagnosis or detection of a long term trend. In each case, optimal analytic goals differ, depending on the relative sizes of physiologic variances to each other and to current analytic precision. Thus, for the first time, a formal, quantitative basis has been established for analytic goal-setting, useful to manufacturers, regulatory agencies and practicing physicians or clinical chemists.

A problem underlying comparisons of biological and analytic variances estimated from real data has been the implicit assumption that long-term analytic variances estimated from quality control or serum pool results are of the same magnitude as the analytic variances affecting serial measurements of blood constituents in patients. To test this assumption, a study was designed in cooperation with Dr. G. Z. Williams (see above) in which long-term analytic and biological variances were separately estimated from analyses of weekly subject

samples split into 3 parts: one portion analyzed as collected, one a
week later, and one stored under deep freeze and not analyzed until the
end of the study.   These long-term analytic variance components were
then compared with those observed in concomitant analyses of serum
pools.   Results (Ref. 3) showed that in all analytes tested except
magnesium and alkaline phosphatase, the serum pool variance was an
adequate representation of the technical variance associated with
analysis of patient sera.   Further studies would be very helpful to
confirm and extend these findings, but such studies must be carefully
designed and are time consuming and unattractive to clinical
scientists, although critical to the unbiased estimation of analytic
variance in patient samples.

Analysis of a relatively large-scale study of intra- and
inter-individual biological variance, undertaken in cooperation with
Dr. S. S. Brown and staff of the Clinic Research Centre, Medical
Research Council, Harrow England (and described in last year's report)
has been completed up to the publication of a first report (Ref. 4).
This has included estimation of the ratio of intra- to inter-individual
variances in ten common serum constituents during a 5-6 month period of
weekly blood sampling from 37 healthy male volunteers aged 23-57 years.
In this study the problems of estimating long-term analytic varation
were avoided by storage at -20 C of all serum specimens, with
analysis in a single 4-hr. run on a multi-channel high-capacity
analyzer at the conclusion of the study.

Significance to Biomedical Research and Mission of DCRT:

The definition and estimation of analytic and biological variance
components provides an essential basis to the objective interpretation
of clinical laboratory tests in patients and healthy persons alike.
The development, testing and eventual routine use of stochastic models
to describe and forecast sequential results of laboratory tests in
individual cases has already proven useful when applied to periodic
monitoring of healthy individuals as part of a general program of
preventive medicine.   These methods of data analysis require the use of
standard computer program packages as well as construction and
implementation of special algorithms for computer-based laboratory
reporting systems.   A spin-off from these research efforts has been the
development of versatile computer systems for storing, updating and
retrieving serial information on multiple laboratory results for
individual patients.   These systems are currently being employed in the
Hypertension-Endocrine Branch (NHLBI) and the Arthritis and Rheumatism
Branch (NIAMDD).   These developmental and associated consulting
activities have expanded the services which DCRT offers the NIH
clinical community.

Future Course:

Statistical analysis of the data received from the Institute of Health Research will continue, as described above. In addition, the requisite statistical theory will be constructed and, where necessary, simulation trials run to determine the power of various stochastic models to detect step changes and nonrandom trends in short series. It is likely that the most powerful trend-detector must include an adaptive slope parameter. Data collected through the joint study with the Clinical Research Centre at Harrow are admirably suited to a test of theoretical methods for using population-based reference distributions to improve the precision of serial results from single individuals. The applicability of such methods and the possibilities of more powerful statistical forecasting models for short series will be studied intensively during the coming year.

Finally, it is anticipated that collaborative studies of normal variations with clinical scientists in Sweden and Japan, still at the discussion stage during this reporting year, will become more active next year.

Publications:

1. Harris, E.K: Some theory of Reference Values, II. Comparison of some statistical models of intra-individual variation in blood constituents. <u>Clin. Chem.</u>, 22, 1343-1350 (August, 1976).

2. Harris, E.K: Statistical principles underlying analytic goal-setting in clinical chemistry. <u>Proceedings of the 1976 Aspen Conference of the College of American Pathologists on Analytical Goals in Clinical Chemistry</u> (in press).

3. Williams, G.Z., Harris, E.K., and Widdowson, G.M: Comparison of estimates of long-term analytical variation derived from subject samples and control serum. <u>Clin. Chem.</u>, 23, 100-104 (January, 1977).

4. Pickup, J.F., Harris, E.K., Kearns, M., and Brown, S.S: Intra-individual variation of some serum constituents and its relevance to population-based reference ranges. <u>Clin. Chem.</u> 23, 842-850 (May 1977).

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00033-01 LAS

PERIOD COVERED

July 1 1976 to September 30 1977

TITLE OF PROJECT (80 characters or less)

Analysis of Coupled Transport and Biochemical Kinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: B. Bunow   Senior Staff Fellow   LAS DCRT

OTHERS: J. Heller   Graduate Student, G. W. University
         J. Kernevez   Prof., Univ of Tech., Compeigne, France
         J. DeSimone   Prof., Univ of Va. (Medical College)
         D. Mukulecky   Prof., Univ of Va. (Medical College)
         J. Rinzel   Mathematician   NIAMDD
         H. Othmer   Prof., Rutgers Univ.

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Applied Mathematics Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, Md 20014

TOTAL MANYEARS: 1.2	PROFESSIONAL: 1.2	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project investigates two fundamental problems in biology: (1) energetics of active transport mechanisms and (2) the role of dynamic patterns in embryological and evolutionary biology. The first area is being examined to determine the adequacy of linear models and the need to incorporate nonlinear aspects of transport processes and biochemical kinetics in membranes. Electrical coupling can replace macromolecular interactions in transmitting chemical energy to transport processes. The second area involves the demonstration of spatial and temporal organization of arrays of cells and immobilized enzyme membranes into differentiated states with various patterns determined by symmetry principles. Bifurcation theory and digital computer simulations are the principal tools of these investigations.

This project was previously reported (FY 76) under ZO1 CT 00005-06 with the subtitle Multiple Steady States of Enzyme Kinetics in cells.

Background and Objectives:

The objectives of this investigation are twofold. The first is a study of dynamic patterns in reaction-diffusion systems obeying realistic biochemical kinetics. The objective here is to demonstrate the existence of solutions to the descriptive equations of these systems in which an unperturbed, homogeneous solution becomes spatially nonhomogeneous or oscillates in time (or both). An experimental model is available to constrain the theory and for which theoretical analysis is required to select proper parameter values. The model is an immobilized enzyme membrane, which by selection of enzyme and membrane structure can represent either a pair of interacting cells or a tissue. Theoretical analysis of this system consists of linearization, stability and bifurcation studies, as well as numerical solution of the describing nonlinear ordinary or partial differential equations.

Progress in FY 77 and Significance to Biomedical Research:

The significant result here is the finding that communication between identical cells leads spontaneously to the development of spatial patterns of non-uniform concentration. The patterns which appear are similar to those seen in embryonic development (partition of blocks of cells into distinct regions whose shape reflects the symmetry of the blocks and the associated patterns of intercellular communication). Such non-uniform concentration profiles could provide a chemical signal to stimulate differentiation of the cells in different directions through their interaction with the genetic control system. This work has been described in presentations, and manuscripts have been published or are in press.

Background and Objectives:

A second direction of investigation is the role of reaction-diffusion processes in membrane transport and energy metabolism. The objective here is to demonstrate that macroscopic considerations, i.e., symmetry conditions and conservation laws, suffice to construct functioning analogs of these biologically important processes. Since experiments in these areas are most often insensitive to molecular process, this mode of description may be more appropriate than one which hypothesizes the existence of complicated molecular "machines".

Significance to Biomedical Research:

This research project seeks a theoretical basis for active transport mechanisms which remain experimentally unresolved despite many years of experimental effort. The present efforts attempt to define the necessary and sufficient principles of operation of any active transport system. This simple minimal mechanism approach with emphasis on nonlinear aspects of the interactions is expected to reveal how energy can be supplied to active transport systems.

Progress in FY 77:

A linear theory has been developed, along the lines of nonequilibrium thermodynamics, but not subject to the restricted conditions of validity of that description. In this theory, a generalization of the Curie principle has been found which restricts the class of systems which can perform active transport or chemosmosis on the basis of their symmetry. Nonlinear extensions of this theory demonstrate the existence of active ion transport processes in which the connection between the input of metabolic energy and the performance of transport work is electrical rather than molecular. This possibility would not be recognized by current experimental technique, showing the need for new kinds of experiments in this field. This work has resulted in new publication and subsequent manuscripts are in press or nearing completion.

Proposed Course:

Future efforts will concentrate on the first problem area. The transition between one or two cells and a whole tissue will be investigated by considering arrays of 4 cells. Specific application to morphogenesis in fruitfly imaginal disk will be actively pursued.

Publications:

1. Bunow, B. Chemically Differentiated States of a Linear Array of Cells with Enzyme-Catalyzed Reaction. Proceedings of the Biophysical Society, February 1976, (abstract).

2. Bunow, B. and DeSimone, J.A. How is Metabolic Energy Coupled into Active Ion Transport? Biophysics of Membrane Transport, Part II (in press) Agricultural Univ. of Wroclaw

3. Bunow, B. and Caplan, S.R. Chemical Reactions and Membranes. Biophysics of Membrane Transport, Part I, 9-30, Agricultural Univ. of Wroclaw, 1976.

4. Bunow, B. Chemical Reactions and Membranes: A Macroscopic Basis for Facilitated Transport, Chemiosmosis, and Active Transport. Part I: Linear Analysis. (Submitted to Biochemistry 1977).

5. Bunow, B. Spatial Patterns from Biochemical Kinetics with Embryological Applications. (abstract) Gordon Research Conference on Theoretical Biology and Biomathematics June 1977.

6. Bunow, B. and Heller J. Spatial Differentiation in an Oscillatory Biochemical Model. Proceedings of Amer. Council on Engineering in Medicine and Biology, Nov 1977 (abstract).

7. Kernevez, J.P., Bunow, B., Duban, M.C., Joly, G. and Thomas, D. Structuration en Espace Spontanee a l'Interieur d'une Membrane Mono-Enzymatique. <u>C.R. Acad. Sci. Paris</u> 284A, 195-198, 1976.

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Computer-based Modeling of Pulmonary Gas Exchange and Respiratory Mechanics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:
J.J. Bailey — Head Medical Appl. Section — LAS DCRT
B.J. Bunow — Senior Staff Fellow — LAS DCRT
J.E. Fletcher — Head, Applied Math. Section — LAS DCRT
B.L. Line — Senior Assistant Surgeon — LAS DCRT
R.G. Crystal — Chief, Pulmonary Branch — NHLBI

OTHERS:
E.K. Harris — Chief, LAS — LAS DCRT
M.R. Horton — Computer Systems Analyst — LAS DCRT
E.W. Pottala — Engineer — LAS DCRT
A.E. Jones — Asst. Chief, Diagnostic Imaging — CC
J.D. Fulmer — Chief, Pulmonary Laboratory — PB NHLBI
B.D. McLees — Staff Cariologist — PB NHLBI

COOPERATING UNITS (if any)

Diagnostic Imaging Branch — CC
Pulmonary Branch — NHLBI

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Applied Mathematics Section, Medical Applications Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS: 2.0	PROFESSIONAL: 2.0	OTHER:

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☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This collaborative effort of three organizations is directed toward a deeper understanding of pulmonary pathophysiology through the construction of computer-based models of pulmonary gas exchange and respiratory mechanics and the comparison of model predictions with real patient data.

Background and Objectives:

Numerous attempts have been made in the past to quantify pulmonary function. Inhomogeneities in the lung required certain simplifying assumptions to be made which tended to obscure the true nature of lung function. Furthermore, certain nonlinearities inherent in the lung system allowed only partial quantitative models and sometimes these could only be expressed in the form of nomograms or graphs.

Within recent years this has been changed by the advent of the digital computer and also by newer diagnostic tools, viz: pulmonary scintillation, cardiac catheterization, multiple inert tracer gas analysis and dynamic compliance studies.

This program involves the Pulmonary Branch, NHLBI; the Diagnostic Imaging Department, CC; and the Laboratory of Applied Studies, DCRT. The objective is to construct computer-based models of pulmonary gas exchange and respiratory mechanics founded upon sound physiological considerations and descriptive mathematical formulations.

Progress during FY 77:

Scintillation data has been used to estimate regional distributions of ventilation-perfusion (V/Q) ratios in the lung in over 300 patients. Concurrently, the Kelman equations for computer-generation of O_2-CO_2 isopleth diagrams were implemented on the PDP-10 system. Subsequently the algorithm was made efficient enough to be translated for the HP minicomputer system in the Diagnostic Imaging Branch.

The regional V/Q distributions were combined with the Kelman algorithm to estimate regional distributions of partial gas pressures-(viz, pCO_2 and pO_2) and blood contents in the lung. In a few cases the regional blood contents were multiplied times the regional perfusions (expressed as a fraction of the total cardiac output) and summed to predict the systemic value which compared well with the value observed in brachial artery samples (ref. 1).

Careful examination of the Kelman programs reveals a number of improvements which could be made. For example, the saturation equation could be modified to use real binding constants instead of empirical coefficients. Several equations contain both unnecessary corrections and sources of numerical imprecision. Some formulae require verification. And finally, the iterative scheme involving three different subroutines is an inefficient algorithm and unnecessarily costly in computer time.

West's model of the lung uses the Kelman program and log normal distributions of V/Q ratios to predict global parameters of lung function. Examination of West's model has revealed certain simplifying

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assumptions, such as continuous (i.e. non-tidal) ventilation; furthermore, the mathematical method for deriving log normal V/Q distributions from patient data is questionable.

Significance:

These computer-based models when combined with data from scintillation, cardiac catheter, and pulmonary laboratory studies should allow a quantitative description of pulmonary pathophysiology on a regional basis. They should allow separation of diseases (e.g., bronchitis from emphysema), separation of disease components (obstructive vs. restrictive vs. vascular), assessment of severity of disease component, and prediction of the degree to which each component compromises overall pulmonary function.

Proposed Course:

A more realistic and more comprehensive model of hemoglobin-saturation kinetics based on the Adair binding constants and data from patients with hemoglobinopathies will be constructed. Kelman's procedure is being revised to incorporate the new model for hemoglobin binding, to remove unnecessary corrections in the formulae and also sources of numerical imprecision, and to utilize more efficient computer algorithms. The simplifying assumptions utilized by West, Wagner, and others will be scrutinized to see if they are necessary and the extent to which they affect results. Alternatives to the methods of Kelman, West, and Wagner will be sought in the literature or may be developed de novo.

Data from scintillation studies, from the cardiac catheter lab, and from the pulmonary laboratory in patients who are at rest or exercising, with varying types and severity of pulmonary disability, with or without therapeutic intervention will be used at every step in the evolution of the models to ensure their clinical relevance and utility.

Dynamic compliance data is recorded onto analog tape in the Pulmonary Laboratory. This data will be digitized and processed by the LAS minicomputer system to provide calculations of compliance and also graphs of pressure-volume relationships at varying respiratory frequencies.

Publications and Abstracts:

1. Line, B.R., Dayhoff, R.E., Bailey, J.J.: An algorithm for the production of regional gas partial pressures and blood contents from scintigraphic and physiologic data using an alveolar gas exchange model. Proceedings of The Seventh Symposium on Sharing Computer Programs and Techology in Nuclear Medicine. Society for Nuclear Medicine, 475 Park Avenue South New York, N. Y., 10016 1977 (in press).

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PERIOD COVERED
July 1 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less):

Mathematical Models and Simulation Programs in Physiology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: E. Hill Jr.   Computer Scientist, AMS   LAS DCRT

OTHERS: J. Fletcher   Mathematician, AMS   LAS DCRT
         E. Harris   Statistician, Chief   LAS DCRT
         C. Tidball   Professor, G.W. Univ.
                              Dept. Physiol.

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Md.   20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

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☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has as an objective the identification of the various simulation programs used in physiology. These programs are to be examined for utility in a clinical environment, accuracy of representation of normal and abnormal physiologic conditions, and the identification of areas of defective or missing physiologic relationships. A general framework for the evaluation and examination of such programs has been studied under contract, and a number of candidate programs are being considered for evaluation.

Objectives:

The objectives of this project are to develop mathematical models of biomedical processes which can be used to explain, interpret and/or predict physiological behavior and limits and to simulate laboratory or clinical experiments. Such models provide a framework for a better understanding of basic biological processes and thereby suggest new approaches to problems of biomedical and biochemical importance. Because of the obvious limitations of manpower and facilities, only a few such models can be considered in depth. These are detailed in the following paragraphs.

Background:

The research area that stimulated the establishment of this project is that of Mathematical Models of Macromolecule-Ligand Binding Equilibria, which has been investigated since 1966. This continuing effort has revised many of the concepts related to the binding of ligands to macromolecules and has produced an interactive methodology for the fitting of models to data and other computer oriented tools for the analysis of data from laboratory experiments.

Significance to Biomedical Research:

The fitting of models to experimentally obtained data is a procedure used to determine unknown parameters in mathematical models. The proper choice of a model and the ability to determine the unknown parameters is a basic tool of biomedical research. Such procedures broaden biomedical knowledge and add to basic scientific knowledge only if the models represent the underlying biologic process, and the unknown parameters can be readily and accurately determined. A thorough and continuing critique of such models and their validity for the interpretation of current laboratory and clinical experiments is therefore essential to the progress of science.

Progress in FY 77:

The most recent efforts in the area of Equilibrium Binding Models have resulted in a single mathematical formulation which includes two models previously used to interpret data. One consequence of this development is the suggestion that many of the past and current literature analyses of data used in the interpretation of macromolecule-ligand binding experiments may be faulty because of the incorrect use of a binding model. For example, such studies are often used to infer the in vivo persistence of drugs in the blood stream and thereby in the design of slow acting or persistent drugs. It has also been demonstrated that nonunique models can be constructed and that some parameters in these models do not represent true properties of binding sites. Publications describing these findings are in press.

Proposed Course:

Further activities in this area, subject to manpower limitations, will develop general purpose computer programs and documentation to explain and implement the practical aspects of the theoretical development. These analytical tools are expected to improve the analysis of drug and other macromolecule-ligand binding analyses.

Background:

The mathematical modeling of substrate supply to tissue from the microcirculation has been under study since FY 69, and several developments have been reported in previous years. The tissue substrate of primary concern is tissue oxygen. Such studies have as an objective the predictions of threshold and critical limits of substrate supply necessary to sustain cell function under a variety of physiologic conditions. The responses to varying blood flow, hemoglobin characteristics, tissue metabolic rate and other physiologic parameters have been examined. The models of these phenomena require the solution of coupled distributed parameter models which are a nonlinear type. The complex interaction of microcirculatory geometry, nonlinear oxygen dissociation properties, and substrate dependent metabolic rates require such a detailed description to achieve physiologic validity.

Significance to Biomedical Research:

Such modeling is necessary to determine the local tissue microcirculatory dynamics since direct measurements are generally not possible and microcirculatory function must be inferred from boundary observations. Studies of this type are used to predict tissue oxygenation during ischemia, hypoxia, anemia, coronary obstructions, Sickle Cell and other conditions of substrate pathophysiology. Recent results have described the effects of red cell metabolism on adaptation to changing oxygen supply conditions such as long term ascent to altitude.

Progress in FY 77:

The mathematical modeling of substrate supply in the microcirculation is currently being applied to concepts of blood oxygenation in the lung. This project is discussed in detail elsewhere. An additional effort is underway to review conceptual models in this area and to identify the respective tissues in which they are most applicable. These efforts will result in improved models for examining substrate supply to various tissues and their controlling factors. An invited publication resulting from this review is in progress.

Background:

A topic area related to the above, but requiring separate lines of investigation is the numerical (approximate) solution of distributed parameter models of substrate transport and diffusion.

Significance to Biomedical Research:

This research topic is related both to the modeling of blood flow in the circulatory system, flow and exchange of gases in the pulmonary system, and any other process where flow and diffusion combine to transport a substrate to the metabolic site. A key to parametric exploration of such models is clearly the ability to efficiently solve the model equations. The collection of such techniques also makes them available to the NIH biomedical community for general use.

Progress in FY 77:

Numerical methods for solving transport and diffusion equations on a computer are being surveyed, and those methods most appropriate for biological transport are being adapted to computer programs. Several techniques are currently being tested, and the most promising methods are being adapted to models under study.

Proposed Course:

These programs can be used in more broadly based studies as well as in the above applications, and will form the basic tools for computing solutions to such models. Efficient and easy to use numerical methods will reduce the cost and decrease the time necessary to simulate a laboratory test or wet lab experiment. This effort will continue at a low level of effort subject to priorities and manpower.

Publications:

1. Fletcher, J.E.: Some Model results on Hemoglobin Kinetics and its Relationship to Oxygen Transport to Blood. Oxygen Transport to Tissue-II edited by J. Grote, D. Reneau, and G. Thews, Plenum Press, New York 1976, Vol. 75, 251-259 (reported in press in FY 76).

2. Fletcher, J.E. and Spector, A.A.: Alternative Models for the Analysis of Drug-Protein Binding. Molecular Pharmacology, Vol. 13, 387-399, May 1977.

3. Spector, A.A. and Fletcher, J.E.: Nutritional Effects on Drug-Protein Binding. Nutrition and Drug Interrelationships, Academic Press, (to appear in 1977).

4. Fletcher, J.E.: A Generalized Approach to Equilibrium Models. Jour. of Physical Chemistry, (to appear in 1977).

5. Spector, A.A. and Fletcher, J.E.: Transport of Fatty Acid in the Circulation. The Physiology of Lipids and Lipoproteins in Health and in Disease. editors J.M. Dietschy, J.A. Dietschy, J.A. Ontko, and A.M. Gotto, American Physiological Society, (to appear in 1978).

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities   1. DCRT

2. PHYSICAL SCIENCES LABORATORY   3. George Weiss
                                                   Chief

I. SUMMARY

Function

The Physical Sciences Laboratory has three principal functions:

- to carry out research in the physical sciences in order to understand biological phenomena in terms of physics and chemistry

- to develop the theory and practical instrumentaion for biomedical experiments, and in particular to relate these to the capabilities of modern computer technology

- to provide consulting services to other scientists at NIH in physics, theoretical chemistry, and several fields in applied mathematics.

The staff of the Physical Sciences Laboratory consists of six professionals who work in the areas of general biophysics, nuclear magnetic resonance, applications of light scattering techniques in biomedical experiments, the physical chemistry of polyelectrolytes and problems in applied mathematics.

Scope of Work

The Physical Sciences Laboratory has several continuing research projects in addition to its consulting services. These projects involve collaborative research with approximately ten other investigators both on and off campus. Two sets of investigators off campus are carrying out experimental work in order to verify theoretical findings by members of the PSL and to apply the theory to biological systems.

Highlights of the Year's Activities

The Physical Sciences Laboratory has had a fruitful and productive year both in the continuation of projects started earlier and also in the successful initiation of two new projects. Drs. Nossal and Brenner have developed instrumentation and theory for measuring elastic properties of gels by laser light scattering techniques. These methods can be contrasted

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with more classical techniques which take orders of magnitude more of time
to make the same measurements.   In the coming year several investigators
at NIH will join Drs. Nossal and Brenner in measuring elastic properties of
biological materials with the system they have developed. Dr. Parsegian's
project on the delineation of forces important in biological interactions
has had a year of continuing success in experimental confirmation of theoretical
work developed in the PSL. Professor Peter Rand of Brock University has
made measurements of forces in membranes at tens of angstroms, using techniques
suggested by Dr. Parsegian that combine x-ray scattering and thermodynamic
analysis. This is the first time that such measurements have been successfully
made in systems of biologic interest.   Dr. David Gingell at the University
of London has confirmed, by ingenious experimentation, that electro-
magnetic forces are effective in holding cells to surfaces at distances of
thousands of angstroms.   These measurements confirm theoretical predictions
developed jointly by Drs. Gingell and Parsegian. Drs. Ferretti and Weiss
have developed a statistical theory that allows an experimenter to decide
on an optimal design for measurements of spin-lattice relaxation times.
Presently there there are large numbers of such experimental designs in the
literature and no way of deciding between them.   In the coming year the
theory will be extended to cover many more cases of experimental interest.
The same type of theory can be used to optimize design parameters for
enzyme kinetic experiments. If time allows, this extension will be made.

In recognition of his many contributions to biophysics, Dr. Parsegian was
appointed editor of the Biophysical Journal for a three year term.   Professor
David O. Tinker of the University of Toronto is spending a sabbatical year
in the PSL working with Dr. Parsegian on electrostatic interactions in
proteins. Dr. Ivan Darvey of the University of Sydney is spending a sabbatical
year with Dr. Weiss working on statistical problems related to enzyme
kinetics experiments.

Measurement of Gel Properties by Laser. As a part of a continuing project
on the application of different optical techniques to problems in the
biological sciences, Drs. Nossal and Brenner have developed a technique for
the measurement of elastic coefficients of gels.

A mathematical theory was developed to interpret light scattering spectra
from elastic media subject to mechanical excitation. Confirmatory experiments
were performed using a specially designed inelastic light scattering
spectrometer.

Experiments suggested by Dr. Parsegian and performed by Dr. David Gingell
at the University of London have shown that cells can be held to surfaces
by long range electromagnetic forces which have been shown to be effective
at distances of thousands of angstroms. Another problem that has been
treated quite successfully is that of calculating the long range forces
between speherical particles extremely accurately.   An exact result is
known for such inter-actions but the resulting series are uncomputable.
Mr. Kiefer has shown that one can approximate the exact result to within
better than 2% accuracy with a series that can be evaluated by hand.

Optimum Strategies for Spin-Lattice Relaxation Time Measurements.
Drs. Ferretti and Weiss have developed a theory of the optimal design of
nuclear magnetic resonance experiments for the measurement of the spin-
lattice relaxation time, T_1. The theory is based on linearized least
squares analysis and allows the experimenter to decide which type of experiment
will be most accurate for fixed experimental time, or which experiment will
have the shortest running time for a given accuracy. Furthermore, for a
given experiment, it leads to nearly optimal specification of the times at
which measurements should be made.

II. PSL PROJECTS AND ACTIVITIES FY 77

Theory of Biochemical Separation Techniques. George H. Weiss, PSL, in
collaboration with Dr. D. A. Yphantis, University of Connecticut. This
project develops mathematical theory for the planning and interpretation of
experiments with such techniques as chromatography, electrophoresis, and
ultracentrifugation.

The Role of Electrostatic Forces in the Organization and Properties of
Macromolecular Systems. Stephen L. Brenner, PSL, V. A. Parsegian, PSL.
This project studies the role of electrostatic forces in determining the
mutual arrangement and interaction of macromolecules in aqueous salt
solutions.

Theory and Application of Nuclear Magnetic Resonance. James A. Ferretti,
PSL. New techniques for carrying out NMR experiments are devised in this
project together with new numerical methods for processing data from this
type of experiment.

Correlation Function Spectroscopy/Laser Light Scattering. Ralph J. Nossal,
PSL, Stephen Brenner, PSL. The laser inelastic light scattering spectrometer
is being used to measure elastic parameters of gels as well as parameters
of cell motility. Several collaborative experiments are being planned
using optical techniques developed by this project.

Cell Motility and Chemotaxis. Ralph J. Nossal, PSL, Stephen L. Brenner, PSL
and George H. Weiss, PSL. This project develops methodology for the
interpretation of experiments related to cell locomotion and chemotaxis.

Theory and Measurement of Intermolecular Forces. V. A. Parsegian, PSL,
George H. Weiss, PSL, James E. Kiefer, PSL. The object of these studies is
to develop the theory of electrodynamic forces in biological media, and to
develop experimental methods for measuring these forces.

Consulting Services. George H. Weiss, PSL, Ralph J. Nossal, PSL, James E.
Kiefer, PSL. Members of the PSL give consulting assistance to other
scientists at NIH and elsewhere, in the areas of the physical sciences and
applied mathematics.

III. PUBLICATIONS

Blumenfeld, D. E., Weiss, G. H.: Sampling errors in the measurement of traffic noise. _J. Sound and Vib._ (to appear).

Brenner, S. L. and Nossal, R. J.: Correlation functions for light scattering from soft gels. _Macromolecules_ (in press).

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Brooks, R. A., Weiss, G. H.: Interpolation problems in image reconstruction. _Applic. of Opt. Instr. in Med._ V. 96, 313–319 (1976).

Correia. J. J., Johnson, M. L., Weiss, G. H., Yphantis, D.: Numerical study of the Johnston-Ogston effect in two component systems in Proceedings of the Conference on _Fifty Years of the Ultracentrifuge_, 255–264 (North-Holland Publishing Co., Amsterdam) 1976.

Correia, J. J., Weiss, G. H., Yphantis, D. A.: An extrapolation method for reducing equilibration times in sedimentation equilibrium experiments. _Biophysical Journal_ (to appear).

Cowley, S., Fuller, N., Rand, R. P., Parsegian, V. A.: Measurement of repulsion between charged phospholipid bilayers. _Biophys. J._ 17, 85a (1977).

Dishon, M., Weiss, G. H.: A Model for burn-in programs for components with eliminateable defects _IEEE Trans. on Reliability_ R-25, 259–260 (1976).

Dishon, M., Weiss, G. H.: When do transient double peaks occur in pH gradient electrophoresis? _Analytical Biochemistry_ (to appear).

Ferretti, J. A., Ernst, R. R.: Interference effects in NMR correlation spectroscopy of coupled spin systems. _The Journal of Chemical Physics._ 65 4283–4293 (1976).

Gingell, D., Parsegian, V. A., Todd, I.: Experimental evidence for long-range attraction between a red cell and a hydrocarbon surface. _Nature_ (in press) (1977).

Hoel, D. G., Weiss, G. H.: Properties of noise emitted by vehicular queues. _Transp. Res._ 11, 39–44 (1977).

Hoel, D. G., Simon, R., Weiss, G. H.: Sequential tests for composite hypotheses with two binomial populations. _J. Roy. Stat. Soc._ B 38, 302–308 (1976).

Kiefer, J. E., Parsegian, V. A., Weiss, G. H.: An easily calculable approximation for the many-body van der Waals attraction between equal spheres. J. Coll. Int. Sci. 57, 580-582 (1976).

LeNeveu, D. M. Rand, R. P., Parsegian, V. A., Gingell, D.: Measurements and modification of forces between lecithin bilayers. Biophys. J. 18, 209-230 (1977).

Lewis, M. S., Weiss, G. H. (editors): Proceedings of the Conference on Fifty Years of the Ultracentrifuge, (North-Holland Publishing Co., Amsterdam) 1976.

McNeil, D. R., Weiss, G. H.: A large population approach to estimation in Markov population models. Biometrika (to appear).

Nossal, R. J., and Chang, Y. T.: A procedure for determining mobility parameters for cells moving along surfaces. J. Mechanochem. Cell Mot. 3, 247-251 (1976).

Nossal, R.J.: Directed cell locomotion arising from strongly biased turn angles. Math. Biosci. 31, 121-129 (1976).

Nossal, R. J., and Zigmond, S. H.: Chemotropism indices for polymorpho-nuclear leukocytes. Biophys. J. 16, 1171-1182 (1976).

Nossal, R. J.: Mathematical analysis of a capillary migration assay for cellular immune sensitivity. J. Theoret. Biol. 64, 703-722 (1977).

Nossal, R. J.: Factors affecting the reliability of capillar MIF (Migration Inhibition Factor) assays. in Theoretical Immunology, ed. I. Bell, A. S. Perelson and G. H. Pimbley, Marcel Dekker, N.Y. (in press).

Oppenheim, I., Shuler, K. E., Weiss, G. H.: The Master Equation in Physical Chemistry. (M.I.T. Press, Cambridge, Mass.) 1977.

Oppenheim, I., Shuler, K. E., Weiss, G. H.: Stochastic theory of nonlinear rate processes with multiple stationary states. Physica (to appear).

Parsegian, V. A., Weiss, G. H., and Schrader, M. E.: Macroscopic continuum model of influence of hydrocarbon contaminant on forces causing wetting of gold by water. J. Coll. Int. Sci.(in press) (1977).

Rubin, R. J., Mazur, J., Weiss, G. H.: Spans of polymer chains, Pure and Appl. Chem. 46, 143-148 (1976).

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Shinnar, R., Weiss, G. H.: A note on the resolution of two Gaussian peaks. Separation Science 11, 377-383 (1976).

Simon, R., Hoel, D. G., Weiss, G. H.: The use of covariate information in the sequential analysis of dichotomous response experiments. Comm. in Stat. (to appear).

Weiss, G. H., Rodbard, D.: Measures of resolution for multicomponent systems in one and two dimensions with application to pore gradient electrophoresis. Separation Science 11, 347-359 (1976).

Weiss, G. H.: The two-state random walk. J. Stat. Phys. 15, 157-165 (1976).

Weiss, G. H., Rubin, R. J.: The theory of ordered spans of unrestricted random walks. J. Stat. Phys. 14, 335-352 (1976).

Weiss, G. H., Dishon, M.: A note on the kinetics of emulsion polymerization. J. Chem. Soc. Faraday Trans. I., 72, 1342-1344 (1976).

Weiss, G. H.: Comments on a model of polymer growth. J. Coll. Interf. Sci. (to appear).

Weiss, G. H., Brooks, R. A.: Integration errors in image reconstruction of circularly symmetric objects. in Theory and Applications of Statistical Mechanics (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00014-10 PSL

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)
Theory of Biochemical Separation Techniques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. H. Weiss	Chief, Physical Sci. Lab.	PSL,DCRT
Other:	D. A. Yphantis	Professor of Biology University of Connecticut	
	R. Shinnar	Professor of Chemistry CUNY	
	M. Dishon	Research Fellow, NASA	

COOPERATING UNITS (if any)

None

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.15	0.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project explores applications of mathematical techniques to biochemical separation techniques such as <u>electrophoresis</u> or <u>ultracentrifugation</u>. Two projects were completed. One involved use of mathematical transformations to accelerate <u>sedimentation equilibrium experiments</u>. The second was a derivation of the mathematical condition necessary to produce a double peak in pH gradient electrophoresis

Most of the work reported on in last year's annual report has been finished and submitted for publication. We have derived a mathematical condition on the gradient for two peaks to occur in transient gradient methods. For this purpose diffusion can be neglected. In the coming year one of several projects may be undertaken depending on time available. These include the following:

1. Experimental verification of the utility of the Aitken transformation as a means of accelerating sedimentation equilibrium experiments.

2. A study of a technique of designing overspeeding parameters in sedimentation equilibrium experiments, for accelerating these experiments that take explicit account of the initial uncertainty. To date the over-speeding method has been designed assuming knowledge of the measured parameter. This leads to extremely sensitive designs which are of little practical use. We hope to eliminate some of the sensitivity inherent in such designs.

3. Development of a singular perturbation technique for the equation where $g(x)$ has a zero in the interval of interest. This equation arises in the analysis of biochemical separation systems with gradients.

Keyword Descriptors: Ultracentrifugation, overspeeding, equilibrium sedimentation.

Publications:

Lewis, M. S., Weiss, G. H. (editors): Proceedings of the Conference on Fifty Years of the Ultracentrifuge, (North-Holland Publishing Co., Amsterdam) 1976.

Correia, J. J., Johnson, M. L., Weiss, G. H., Yphantis, D.: Numerical study of the Johnston–Ogston effect in two component systems in Proceedings of the Conference on Fifty Years of the Ultracentrifuge, 255-264 (North-Holland Publishing Co., Amsterdam) 1976.

Weiss, G. H., Rodbard, D.: Measures of resolution for multicomponent systems in one and two dimensions with application to pore gradient electrophoresis. Separation Science 11, 347-359 (1976).

Shinnar, R., Weiss, G. H.: A note on the resolution of two Gaussian Peaks. Separation Science 11, 377-383 (1976).

Dishon, M., Weiss, G. H.: When do transient double peaks occur in pH gradient electrophoresis? Analytical Biochemistry (to appear).

Correia, J. J., Weiss, G. H., Yphantis, D. A.: An extrapolation method for reducing equilibration times in sedimentation equilibrium experiments. Biophysical Journal (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER
		Z01 CT 00017-05 PSL

PERIOD COVERED
July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)
Cell Motility and Chemotaxis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. J. Nossal, Research Physicist	PSL,DCRT
Other:	G. H. Weiss, Chief,	PSL,DCRT
	S. L. Brenner, Staff Fellow	PSL,DCRT

COOPERATING UNITS (if any)

L. Lipkin, M.D., Image Processing Unit, DCBD, NCI
Y. T. Chang, M.D., Laboratory of Biochemical Pharmacology, NIAMDD
S. H. Zigmond, Department of Biology, University of Pennsylvania

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INSTITUTE AND LOCATION

Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.5	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been undertaken to study various aspects of cell locomotion and chemotaxis. A mathematical theory has been devised to relate chemotropism indices to the characteristic random walks of individual cells. Analytical expressions to quantitate capillary migration (MIF) assays have been derived. New procedures for measuring macroscopic coefficients of cell migration are being developed.

Cell Motility and Chemotaxis

This study pertains to phenomena relating to cell locomotion and chemotaxis. Recent emphasis has been on examining immunologic aspects of leukocyte migration. One result is a mathematical theory of interpreting capillary migration assays for cellular immune sensitivity (MIF tests). Also, an analytic theory has been developed to relate the chemotactic response of neutrophil populations to parameters characterizing the stochastic movements of individual cells.

Collaborative experiments regarding leukocyte locomotion have been performed with Drs. Lewis Lipkin (DCBD/NCI) and Sally Zigmond (U. of Pa.). These involve studying the movements of neutrophils when responding to various chemical factors, including substances (lymphokines) produced by stimulated lymphocytes.

Specialized techniques have been devised, an example of which is a scheme where occupation number fluctuations are analyzed to determine mobility coefficients of migrating cells. Recently, we have completed an extensive theoretical analysis of factors which influence the design of such experiments. Computer assisted microscopy techniques currently are being developed which will be used in studies involving the tracking of individual cells.

Publications:

Nossal, R., and Chang, Y. T.: A procedure for determining mobility parameters for cells moving along surfaces. J. Mechanochem. Cell Mot. 3, 247-251 (1976).

Nossal, R.: Directed cell locomotion arising from strongly biased turn angles. Math. Biosci. 31, 121-129 (1976).

Nossal, R., and Zigmond, S. H.: Chemotropism indices for polymorpho-nuclear leukocytes. Biophys. J.16, 1171-1182 (1976).

Nossal, R.: Mathematical analysis of a capillary migration assay for cellular immune sensitivity. J. Theoret. Biol. 64 703-722 (1977).

Nossal, R.: Factors affecting the reliability of capillar MIF (Migration Inhibition Factory) assays. in Theoretical Immunology, ed. G. I. Bell, A. S. Perelson and G. H. Pimbley, Marcel Dekker, N.Y. (in press).

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Correlation Function Spectroscopy/Laser Light Scattering

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. J. Nossal, Ph.D.   Research Physicist   PSL,DCRT
Other: S. L. Brenner, Ph.D.   Staff Fellow   PSL,DCRT

COOPERATING UNITS (if any)

H. Saroff, Ph.D., Laboratory of Biophysical Chemistry, NIAMD
R. Gelman, Ph.D., Laboratory of Biochemistry, NIDR
C. Delisi, Ph.D., Laboratory of Theoretical Biology, NCI

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Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.9	0.7	0.2

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☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Experimental and theoretical studies have been performed in order to develop laser inelastic light scattering techniques for studying biological gels.

Correlation Function Spectroscopy/Laser Light Scattering

A principal objective of this project is the development of laser inelastic light scattering techniques for performing rapid and precise measurements on biological materials. In principle, any process giving rise to refractive index fluctuations can be monitored. For example, concentration fluctuations can be used to determine diffusion coefficients of macromolecules, rate constants of bimolecular reactions, and swimming speed distributions of motile microorganisms.

During the past year we devised a scheme for measuring elastic coefficients of soft biological gels. Materials which can be studied by the technique include cytoplasmic gels, vitreous humor, collagen polymer networks, and fibrin clots. A mathematical theory was formulated to interpret light scattering spectra from finite eleastic media subject to mechanical excitation. Experiments were performed with a specially designed inelastic light scattering spectrometer, in order to test and confirm the theory.

Other experiments were performed on phenonema related to cytoplasmic transport and cell motility. A theoretical analysis has been performed of a laser electrophoresis experiment which might detect rates of certain antigen-antibody reactions. Future instrument development may involve design and construction of apparatus for detecting electrophoretic mobilities and also, instrumentation for performing fluorescence intensity spectroscopy.

Keyword Descriptors:

Laser light scattering, macromolecules, diffusion coefficients, correlation functions, gels.

Publications:

Brenner, S. L. and Nossal, R.: Correlation functions for light scattering from soft gels. Macromolecules (in press).

Brenner, S. L., Gelman, R. A., and Nossal, R. J.: Laser light scattering from soft gels. Macromolecules (in press).

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Theory and Application of Nuclear Magnetic Resonance Spectroscopy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: James A. Ferretti, Ph.D., Research Chemist, PSL,DCRT
Other: E. D. Becker, Chief, Laboratory of Chemical Physics, LCP,NIAMDD
         R. R. Ernst, Professor, Laboratorium fur Physikalische Chemie,
              Eidgenossische Technische Hochschule, Zurich, Switzerland
         G. R. Marshall, Professor of Physiology, Dept. of Physiology,
              and Biophysics, Washington University School of Medicine,
              St. Louis, Mo.
         G. H. Weiss, Chief, Physical Sciences Laboratory, PSL,DCRT

COOPERATING UNITS (if any)

Laboratory of Chemical Physics, NIAMDD

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Div. of Computer Research & Technology, NIH, Bethesda, Maryland

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☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less — underline keywords)

The purpose of this project is to develop new methods in nuclear magnetic resonance spectroscopy and also to apply NMR to the study of small proteins. In particular, development of the correlation method of obtaining NMR spectra is of special interest. An experimental and theoretical study of interference effects in correlation spectroscopy has been undertaken. Saturation effects in correlation NMR are currently being studied. Investigations of the solution conformation of derivatives of Angiotensin and Bradykinin is in progress. Preliminary results show that marked changes in the conformation of angiotensin derivatives occur with very little change in biological activity.

Progress has been made in the study of non-linear interference effects in NMR correlation spectroscopy of coupled spin systems. The two principal types of effects result from passage with transverse interference and from passage with longitudinal interference. In the case of longitudinal interference the transverse components of magnetization completely decay before the next resonance in sequence is excited although longitudinal relaxation is negligible during passage through the spectrum. Here one obtains incorrect relative intensities when strong rf field strengths are employed for spectral excitation. Experiments such as relaxation time and nuclear Overhauser effect studies must be carried out using sufficiently weak rf fields. For the transverse interference effect to occur, both transverse and longitudinal relaxation must be negligible during passage through the spectrum. Here distorted line shapes and intensities will occur except for some discrete values of the sweep rate. Transverse interference is very often accompanied by longitudinal interference, for example, for strongly coupled systems and for systems in a non-equilibrium state. Anomalies occur even in uncoupled spin systems for large rf field strengths when the conditions of fast passage are violated. Studies are in progress to elucidate the nature of saturation effects in correlation spectroscopy.

Spin-lattice relaxation times, T_1, and nuclear Overhauser enhancement factors have been determined on series of Angiotensin II and Bradykinin derivatives. Angiotensin II is a naturally occuring linear octapeptide whose biological activities include reversible blood pressure elevation and smooth muscle contraction. Bradykinin is a linear monopeptide which shows arterial wall and other smooth muscle stimulation. These derivatives contain bulky steric groups located on the polypeptide backbone. In these cases, the NMR studies were carried out in order to infer constraints on the receptor-bound conformation of these hormones. From the T_1 and nuclear Overhauser effect studies we have been able to propose qualitative features of the backbone conformations. These studies show that both the Angiotensin II and the Bradykinin derivatives are flexible in aqueous solution with segmental motion in the peptide backbone. It appears that the correlation times for segmental and overall rotational motion are similar in magnitude in these peptides. The effect of methyl substituents is to reduce the inherent conformational flexibility available to the molecules without significantly altering their biological activity.

We have analyzed various aspects of NMR spin-lattice relaxation time, T_1, studies determined by the inversion-recovery and saturation recovery methods. The purpose of these calculations is to develop a strategy for determining at what values of the time along the relaxation curve data should be taken in order to obtain T_1 with a maximum precision. We find that with a two parameter fit the fast inversion-recovery method seems to be the most efficient. The standard inversion-recovery method is next, with the saturation-recovery method less efficient, provided

that equal spacings of points is chosen. We also conclude that the use
of the exponential fitting procedure is better than the use of the
unweighted log form of the relaxation equation. Our optimization procedure
requires that a reasonably restricted range $T_A < T_1 < T_B$ must be selected.
If this restriction is not available, then a crude determination of T_1
should first be made.

Publications:

    J. A. Ferretti and R. R. Ernst, : Interference effects in NMR
correlation spectroscopy of coupled spin systems. J. Chem. Phys., 65,
4283-4293 (1976).

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Theory and Measurement of Intermolecular Forces

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	V. A. Parsegian	PSL,DCRT
	G. H. Weiss	PSL,DCRT
	D. O. Tinker	University of Toronto
	J. E. Kiefer	PSL,DCRT
Others:	M. Schrader	Naval Weapons Laboratory
	R. P. Rand	Brock University
	L. Lis	Brock University
	S. Cowley	Brock University
	M. McAlister	Brock University
	N. Fuller	Brock University
	D. Gingell	Middlesex Medical School

COOPERATING UNITS (if any)

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Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS: 2	PROFESSIONAL: 2	OTHER: 0.3

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project aims to understand the role of <u>long range forces</u> on biological phenomena. A major topic has been the measurement of forces between <u>phospholipid bilayer membranes</u> immersed in water. We have recently succeeded in measuring intermolecular forces between lipids in the same membrane.

Using the DCRT <u>electronic display</u> we have found two classes of forces between <u>protein molecules</u> forming dimers and tetramers (such as hemoglobin). An accurate procedure for calculating <u>many body</u> forces between spherical particles has been developed.

Theory and Measurement of Intermolecular Forces

We have made good progress in developing methods for computing and detecting intermolecular forces. This has been accomplished in model cell membranes immersed in water, cells adhering to surfaces, protein particles forming functioning dimers and oligomers and in the study of surfaces on which thin films of water will spread.

In the area of force computation, we have developed efficient and accurate methods for deriving forces between spherical particles. Similarly we have determined the influence on the force of polymers coating these particles. Both formulations are useful in understanding colloidal aggregation where van der Waals attraction forces are expected to cause colloidal particles to come together but fudge-free estimates of force magnitude are difficult.

With Professor Peter Rand of Brock University we have successfully made measurements of forces between phospholipid bilayer membranes. This includes several estimates of the van der Waals force between bodies in water. The results published so far are the beginning of a series of systematic studies on the physical properties of cell membrane lipids. We hope to extend these then to direct observations of forces between natural cell membranes. So far we have worked successfully with several model preparations. We have measured, for the first time, the important electrostatic repulsion between charged membranes. We have been able to measure also forces between molecules within the same membrane. This finding has opened up new means to determine the mechanical properties of artificial and natural membranes.

With Dr. David Gingell of London, England we have been studying the interactions of red cells with each other and with artificial materials. Guided by the theory of forces developed in this laboratory we have devised experiments demonstrating that cells can be held to surfaces by long-range electromagnetic forces, which have now been shown to act at thousands of Angstroms separation.

With Dr. Malcom Schrader of the Naval Weapons Research Laboratory we continue to work on the formation of films on clean gold surfaces. We have been able to show why minute amounts of contaminant will spoil the wetting of gold and why earlier theories wrongly described the spread of water on non-aqueous surfaces.

Publications

Kiefer, J. E., Parsegian, V. A., Weiss, G. H.: An easily calculable approximation for the many-body van der Waals attraction between equal spheres. J. Coll. Int. Sci. 57, 580-582 (1976).

LeNeveu, D. M., Rand, R. P., Parsegian, V. A., Gingell, D.: Measurements and modification of forces between lecithin bilayers. Biophys. J. 18 209-230 (1977).

Cowley, S., Fuller, N., Rand, R. P. and Parsegian, V.A.: Measurement of repulsion between charged phospholipid bilayers. _Biophys. J._ _17_, 85a (1977).

Gingell, D., Parsegian, V. A., Todd, I.: Experimental evidence for long-range attraction between a red cell and a hydrocarbon surface. _Nature_ (in press) (1977).

Parsegian, V. A., Weiss G. H. and Schrader, M. E.: Macroscopic continuum model of influence of hydrocarbon contaminant on forces causing wetting of gold by water. _J. Coll. Int. Sci._ (in press) (1977).

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

The Role of Electrostatic Forces in the Organization and Properties of Macromolecular Systems.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: S. L. Brenner, Senior Staff, Fellow,   PSL,DCRT
Other: V. A. Parsegian, Physicist   PSL,DCRT
        R. A. Gelman, Laboratory of Biochemistry   NIDR

COOPERATING UNITS (if any)
Laboratory of Biochemistry, NIDR
David Gingel, Middlesex Hospital, London, England

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS: 5	PROFESSIONAL: 0.4	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the project is to probe the role of electrical forces in macromolecular solutions and in organized macromolecular arrays. Studies of the electrostatic interactions between membranes including image forces have been completed and modifications of previously computed forces have been obtained.   Initial analyses have been made to examine the role of charge-charge interactions in observed properties of polysaccharide-protein solutions in collaboration with R. Gelman of the NIDR. These systems are models for the more complex collagen-mucopolysaccharide matrix found in connective tissue. The precise location and function of the poly-saccharides and their observed strong influence on the helical state of cationic poly-amino acids will be investigated.

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Studies in Mathematics and Statistics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. H. Weiss	Chief, Phys. Sci. Lab.	PSL,DCRT
Other:	D. G. Hoel	Chief, Biometry Branch	EBB,NIEHS
	M. Dishon	Research Fellow	NASA
	D. E. Blumenfeld	Lecturer College, London	University
	R. J. Rubin	Senior Scientist	NBS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.2	OTHER: 0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project includes several unrelated studies in applied mathematics or mathematical statistics. One phase of a study on stochastic and deterministic models for chemical reactions has been completed showing their comparability in the thermodynamic limit. A study was begun of numerical procedures for inverting the Mellin or two-sided Laplace transform.

Studies in Mathematics and Statistics

One phase of the project that compares stochastic and deterministic models for the same phenomenon has been completed. We have resolved seemingly contradictory behavior in these two types of models in one dimension by showing that the stochastic models may have different time scales. In one time scale the stochastic description of the kinetic system nearly coincides with the deterministic description while in the other the stochastic model has an equilibrium state independent of the initial conditions. This may be in contradiction to the deterministic model, but we have shown that the time scale depends on the number of particles in the system. In the limit of an infinite number, the time during which the stochastic model mimics the deterministic one becomes infinitely great.

We have developed a technique for numerical inversion of the Mellin transform. This is done by means of a trapezoidal integration rule for the inversion integral. In connection with this project we have begun to look at numerically efficient ways to sum Fourier series.

A study was completed on sampling estimators for the beta distribution. The maximum likelihood estimator was found to be better than the moment estimator, and more importantly, quite easy to implement numerically.

We have continued to investigate properties of acoustic noise from highway traffic. The problem of calculating the underlying probability from the moments was examined. The most consistent estimate was found to be by means of Pearson curves. In particular, the beta distribution was found to apply to all of the data.

Keyword Descriptors: birth and death processes, Mellin transforms, Fourier series, beta distribution, maximum likelihood estimate, highway noise.

Publications:

Weiss, G. H.: The two-state random walk. J. Stat. Phys. 15, 157-165 (1976).

Weiss, G. H., Rubin, R. J.: The theory of ordered spans of unrestricted random walks. J. Stat. Phys. 14, 335-352 (1976).

Rubin, R. J., Mazur, J., Weiss, G. H.: Spans of polymer chains, Pure and Appl. Chem. 46, 143-148 (1976).

Weiss, G. H., Dishon, M.: A note of the kinetics of emulsion polymerization, J. Chem. Soc Faraday Trans. I, 72, 1342-1344 (1976).

Oppenheim, I., Shuler, K. E., Weiss, G. H.: The Master Equation in Chemical Chemistry. (M.I.T. Press, Cambridge, Mass.) 1977.

Dishon, M., Weiss, G. H.: A model for burn-in programs for components with eliminateable defects. IEEE Trans. on Reliability R-25, 259-260 (1976).

Hoel, D. G., Weiss, G. H.: Properties of noise emitted by vehicular queues. Transp. Res. 11, 39-44 (1977).

Hoel, D. G., Simon, R., Weiss, G. H.: Sequential tests for composite hypotheses with two binomial populations. J. Roy. Stat. Soc. B 38, 302-308 (1976).

Rubin, R. J., Weiss, G. H.: Span of a random flight model of a star-branched polymer chain. Macromolecules 10, 332-334 (1977).

Oppenheim, I., Shuler, K. E., Weiss, G. H.: Stochastic theory of nonlinear rate processes with multiple stationary states. Physica (to appear).

Weiss, G. H.: Comments on a model of polymer growth. J. Coll. Interf. Sci. (to appear).

Simon, R., Hoel, D. G., Weiss, G. H.: The use of covariate information in the sequential analysis of dichotomous response experiments. Comm. in Stat. (to appear).

Blumenfeld, D. E., Weiss, G. H.: Sampling errors in the measurement of traffic noise. J. Sound and Vib. (to appear).

McNeil, D. R., Weiss, G. H.: A large population approach to estimation in Markov population models. Biometrika (to appear).

PERIOD COVERED

July 1, 1976 to September 30, 1977

TITLE OF PROJECT (80 characters or less)

Consulting Services

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. H. Weiss, Chief, Physical Sciences Laboratory, PLS,DCRT
Other: R. J. Nossal, Physicist   PSL,DCRT

COOPERATING UNITS (if any)
W. C. Caveness, M.D.,Chief, Laboratory of Experimental Neurology, NINCDS
E. T. Fischmann,M.D., Department of Cardiology, Howard University
R. Gelman, Ph.D., Laboratory of Biochemistry, NIDR
R. Brooks, Research Physicist, Surgical Nuerology Branch, NINCDS
H. Lecar, Ph.D., Laboratory of Biophysics, NINCDS

SECTION
Physical Sciences Laboratory

INSTITUTE AND LOCATION
Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER: 0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Members of the Physical Sciences Laboratory provide consulting services to the scientists at N.I.H. in the areas of the physical sciences and applied mathematics. A continuing project is the planning of a study of head injured veterans of the Vietnam war to be carried out at a consortium of hospitals. Some work has been done on the development of noise in the EMI scanner. A third project has been on the reduction of data from experiments in nerve regeneration.

Consulting Services

A considerable amount of time was spent on planning a study of head injured Vietnam veterans together with Dr. William Caveness of NINCDS. The initial part of the study consists of summarizing injury and subsequent hospitalization records, and compiling these into a data base. When this job is completed, we will attempt to correlate injury characteristics and treatment with such factors as death, improvement in life quality, or other outcomes deemed relevant. The significance of this study is that the population is both large and relatively homogeneous and may furnish the answers to many presently open questions as to effective treatment for severe head injuries. In the coming year planning will begin on a second phase involving physical examination of as many of the veterans as possible.

Together with Dr. Rodney Brooks of NINCDS we have analyzed the effect of interpolation error on image reconstruction in computerized axial tomography. Our first study was on the effect of linear interpolation on circularly symmetric objects. We have also considered the more general case of asymmetric objects but the calculations are much more difficult in that case.

Dr. Nossal has consulted with Dr. David Forman on analytic problems related to axonal transport and nerve regeneration. A previously devised scheme for estimating the mean length of fibers regrowing from a crushed nerve has been modified in order to provide length distributions from radioactive tracer data. Dr. Nossal also has assisted members of the Laboratory of Biochemistry, NIDR, in developing light scattering of collagen polymerization.

We have helped Dr. Harold Lecar to develop a theory of ion noise in membranes that takes some account of pore structure.

Publications:

Brooks, R. A., Weiss, G. H.: Interpolation problems in image reconstruction. Applic. of Opt. Instr. in Med. V. 96, 313-319 (1976).

Weiss, G. H., Brooks, R. A.: Integration errors in image reconstruction of circularly symmetric objects. in Theory and Applications of Statistical Mechanics (to appear).

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

2. LABORATORY OF STATISTICAL AND

MATHEMATICAL METHODOLOGY

1. DCRT

3. James E. Mosimann

Chief

I. SUMMARY

Function

The Laboratory of Statistical and Mathematical Methodology (LSM) combines research in mathematical statistics, mathematics, computer and information science, with collaboration and service in these areas to NIH researchers and administrators. There are four sections in LSM:

. The Statistical Software Section (SSS) provides consultation to and collaboration with NIH researchers and administrators in all computational aspects of biomedical data analysis, including selection and support of large program packages. Three specialists in scientific programming are led by a computer systems analyst whose specialty is statistics.

. The Biomathematics and Computer Science Section (BCS), directed by a mathematician, performs independent research and provides consultation and collaboration in the specialties of its six mathematicians and computer scientists.

The Statistical Methodology Section (SMS) works closely with the Statistical Software Section. Four individuals who work under the direction of a mathematical statistician provide biostatistical consultation and do independent research.

. The Medical Information Science Section (MIS) investigates and develops methods for application of information and computer science to medical language data processing. Five individuals work under the direction of a computer systems analyst who specializes in computational linguistics.

Scope of Work

LSM staff interact with all NIH institutes and with government agencies outside HEW. Fiscal year 76 was LSM's third year as a separate entity within DCRT.

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The volume of its computational and consultation services continued to expand while its research activities were maintained at about the same level as the preceding year.

Highlights of the Year's Activities

Computation. A very significant part of LSM activity is the offering of statistical and mathematical program packages to the NIH user community. LSM accepts responsibility for evaluation of new program packages and their suitability for NIH. When LSM does offer a package to the NIH community, LSM makes three basic commitments:

. The maintenance of the package, with adequate documentation, through NIH computer system changes, package updates and corrections.

. The rapid response to queries concerning user access to a package program including job control language and program parameters.

. The assistance in interpretation of results.

During this year, as in the past year, SSS maintained the following program packages and programs:

BMD,	Biomedical Computer Programs, UCLA
BMDP,	Biomedical Computer Programs, P-series, UCLA
SPSS,	Statistical Package for the Social Sciences, SPSS, Inc.
SAS,	Statistical Analysis System, SAS Institute, Inc.
PSTAT,	Princeton Statistical Package, Princeton University
IMSL,	International Mathematical and Statistical Libraries, IMSL Inc.
MSTAT1,	Collection of Mathematical and Statistical Programs, DCRT.

The effort expended in the commitment to maintain these packages is considerable. During this year every package went through at least one update, and totally new documentation for MSTAT1, "the DCRT Mathematical and Statistical Program Manual", was prepared and distributed. The effort expended in response to queries concerning package access is also considerable and requires continuous availability. During the year over 3,000 calls were responded to by SSS Staff alone. Two courses were taught on each of the following packages: BMDP, SPSS, and SAS.

The use of program packages has shown considerable increase this year over fiscal 76. The average accesses per month of all the statistical packages rose from 3000 during fiscal 76 to almost 6000 in fiscal 77. SAS experienced the largest increase of any of the packages. SAS averaged over 2000 accesses per month, up from 700 per month in fiscal 76. This increase is attributed to the new version of SAS, SAS76, installed during fiscal 77. The average number of accesses per month for SPSS increased from 1400 to 2600, an increase of 86% over the last year for SPSS. The average combined accesses of the BMDP and BMD packages increased from 800 accesses per month in fiscal 76 to around 900 accesses per month this year. BMDP was up from 360 average

accesses per month in fiscal 76 to 600 average accesses per month this year, while BMD went down from 450 average accesses per month to 300 average accesses per month in the same period of time. As an example of a package used for specialized purposes, PSTAT averaged 30 accesses per month, down from 35 average accesses per month in fiscal 76. The main programs in MSTAT1 averaged 175 accesses per month, an increase of 75% over fiscal 76. The subroutine usage of MSTAT1 which can only be estimated is much higher than the main program usage. Accesses to the IMSL package cannot be counted, but it is estimated that usage increased during fiscal 77.

The Biomathematics and Computer Science Section maintains two computer packages for biomathematical modeling at NIH: MLAB on the PDP-10 and MODELAIDE on S/370. Both packages were developed by BCS staff members and are widely used at NIH and elsewhere here and abroad. MLAB, in particular, is used by hundreds of NIH biomedical researchers, with only occasional contacts with BCS computer specialists needed in most cases. This fiscal year, a capability for 3D computer graphics was added to MLAB. That is, general methods were implemented for creating and modifying images of curved surfaces and other objects in three-dimensional space. The reference manual for MLAB is currently being revised, with documentation for the new capabilities added and many new discussions of MLAB applications included. A separate beginner's guide for MLAB is also in preparation. The MLAB introductory course was taught twice during the fiscal year.

The computer package C-LAB for pattern recognition and cluster analysis was completed during the fiscal year. It was announced to the NIH community and documentation was distributed. C-LAB currently has about 12 NIH users.

The computer package REDUCE for symbolic manipulation of algebraic and differential equation formulas was obtained from the University of Utah during the fiscal year. It was implemented on the PDP-10 with the assistance of the PDP-10 systems team, and was announced for use by the NIH community on a trial basis. Documentation and advice on use of this program are available through the BCS.

Consultation. The diverse nature of LSM consulting is indicated by the projects and activities listed in Part II. This list is a sample of activities and is not exhaustive.

There was a slight change in emphasis of consultation this past year, as compared with the previous two. This is revealed in the pattern below in which percentages on the left represent fiscal years 75 and 76, and those on the right, this past year (77):

. Mathematical or statistical advice with limited computer use	20% →	10%
. Mathematical or statistical advice with considerable computer use	40% →	50%
. Computational advice alone	40% →	40%

This increase to more computer use with consultation is also a reflection of the increased availability and use of statistical packages like SAS. MIS activities, which involve relatively little consultation, are not represented in the above percentages.

As in previous years there was considerable variation in the amount of time required for an LSM consultation. Some very brief consultations are very successful, and are brief precisely because there is a known answer to the statistical/mathematical question posed. Other consultations involve extensive time and statistical/mathematical research as well. One such case, a collaboration on a study of schistosomiasis with Dr. A. Cheever, Laboratory of Parasitic Diseases, NIAID, was discussed in last year's report. This past year saw considerable continued activity on this project for which three papers are currently in press.

Many consultations which involve considerable LSM effort do not involve new statistical research. An illustration is a project of Ms. Ruth Carlsen, Nursing Department, CC. Here LSM reviewed previous research on job-related satisfaction of "team" versus "primary" nurses. (A patient under a primary nursing system is attended to by only one nurse, and under team nursing, by many.) Then both SMS and SSS members participated with Ms. Carlsen in the design and preparation of a questionnaire for a study of job-related satisfaction of team and primary nurses in the clinical center. Extensive statistical analyses of the results were performed, including factor analyses for comparison with previous research results; however, interpretations were finally based on contingency table analysis and non-parametric statistical techniques. Where job satisfaction-level differences were found, team nurses were routinely more dissatisfied than primary nurses.

Research.

BCS research included projects in biomathematics, general mathematical methods, and computer science. A BCS staff member is cooperating in a project for detection of cancer by computer analysis of two-dimensional patterns obtained from a fluorescence-activated cell sorter; this project also involves development and computer implementation of general-purpose mathematical techniques of cluster analysis. Research continued on the "symmetric axis" method of shape description, which is natural for description of biological shapes changing by growth and development. An analysis of relationships between elements of the formal descriptions and qualitative features of the described shapes was published, and computer programs were enhanced and developed. A cooperative study applied these techniques to cleft palate skull measurement data. In another study, computer methods of fitting nonlinear differential equation systems with linear constraints to experimental data were augmented to allow two new fitting criteria: minimum sum of absolute differences (L-one norm) and minimum value of the maximum absolute difference (L-infinity norm). Other studies concerning inclusion relations between subspaces of vector spaces and computer storage and retrieval algorithms are continuing.

In SMS research on multivariate statistical methods, "size and shape" methods continued. An SMS member was invited by CSIRO (The Commonwealth Scientific and Industrial Research Organization) to lecture on these resul in various universities and CSIRO installations in the five major Australi cities.

MIS research activity was still mainly concerned with the automatic processing of natural language medical data. Main effort continued to be devoted to structuring medical microglossaries for use in processing medic texts. Studies included segmentation of medical compound words and evalua of the possible development of a computer-oriented grammar for such processing. The ultimate goal is the development of an information storag and retrieval system for medical records in various world languages.

Future Plans

No major shift in laboratory service or research is anticipated in the comi year. Current levels of support of statistical and mathematical program packages, and consultation and user assistance will be maintained or expand Biomathematical and biostatistical research projects will be continuations of those already initiated and reported here.

II. LSM PROJECTS AND ACTIVITIES

The following list contains major LSM consulting activities of the year.
Then the LSM individual research reports are presented.

DNA distances analysis. R. Martin, LMB, NIAMDD. Distances between strands
of DNA molecules were measured. Twelve samples ranging in size from 200 to
450 measurements were grouped into frequency distributions. It was desired
to test the null hypothesis that the measurements in each pair of samples
were drawn from the same population of measurements. Statistical methods
used included Chi-squared goodness of fit tests, Student's t-tests, and F tests.

Isoproterenol and C-AMP levels in normal and cystic fibrosis families. P. Davis,
PMB, NIAMDD. Levels of Isoproterenol and PGE-triggered C-AMP were studied for
parents of cystic fibrosis patients as compared with parents in normal families.
LSM assisted in statistical analysis by Student's t-tests and analysis of
covariance.

Putresine clearance in normal and cystic fibrosis patients. D. Lundgren, PMB,
NIAMDD. Study of 24-hour creatinine and putresine clearances in urine in
normal controls and in patients with cystic fibrosis, with and without
correction for body surface area. Correlations, t-tests, Wilcoxon rank-sum
test are among the statistical methods used.

Comparison of luminal narrowing of coronary vessels in two kinds of patients.
C. Curry, H IR OD. The degree of luminal narrowing in major coronary vessels
in patients with nephrotic syndrome was compared with the narrowing in normal
patients. Hotelling's T^2 and Chi-squared tests were used.

Poly-U, Poly-C, and Poly-AU differences between smokers and non-smokers.
D. Maor, BCRC, NCI. Differences in levels of Poly-U, Poly-C, and Poly-AU in
blood samples of smokers and of non-smokers were studied. Correlations,
Hotelling's T^2, and discriminant analyses were performed.

Relationship of left atrial-ventricular pressure gradient to other heart
functions. T. Lachman, H IR OD. The data included autopsy reports on
patients with heart disease. The study was principally concerned with
observable pathologies in heart and coronary vessels as related to value of
left-atrial-to-left-ventricular pressure gradient. Chi-square tests were
used in the statistical analysis.

Relationship of mitral annular calcification to other heart pathologies.
W. Muna, H IR OD. Autopsy data on patients with varying degrees of mitral
annular calcification was analyzed. The relationship of the calcification to
other observable pathologies in the heart and coronary vessels was studied.

Sleep analysis. W. Duncan, AP, NIMH. A continuing analysis focuses on
examining the relationship between mental illness and sleep disorders.
Discriminant analysis is employed to evaluate possible contribution of
sleep variables in distinguishing between groups of normal subjects, depressed
(unipolar and bipolar), and insomniac patients.

Iodine metabolism and endemic goiter studies. R. Vought, EFSB, NIAMDD.
The analyses included examination of the principal environmental factors
associated with prevalence of goiter, and the nature of the metabolic
defects responsible for the disease in Greece. Tests were made to demons[
differences in E. Coli antibodies, or between IGA, IGG and IGM serum
concentrations, between the goitrous and nongoitrous, or between endemic a
nonendemic areas. Statistical methods used include analysis of variance,
chi-square tests, and frequency tables.

Cell line discrimination based on chromosome analysis. D. Axelrod, NHLI.
The primary purpose of this project was to distinguish cell populations
on the basis of size and shape quantities derived from counts of chromosom
of a given type. Size and shape as defined in Penrose (1954) and a specia
program written for the Hewlett-Packard 9820 were used in this analysis.

Cook Island filariasis project. P. Weller, NIAID. Filariasis is common
among natives of the Cook Islands. Data was obtained on 400 Cook Islander
70 of whom were treated and then studied intensively. The purpose of the
study was to look for associations between physical variables and laborato
findings that had been hypothesized but never verified. Frequency countin
and correlations were the statistical tools employed. As an example of on
finding, the Cook Islanders scored subnormally on pulmonary function tests
and upon treatment, patients seemed to worsen before improving. This may
indicate a tendency of filaria to become trapped in the lungs as an initia
response to treatment. An intensive amount of programming was required to
reformat the investigator's file so that it would be acceptable to LSMM's
statistical packages. Individual requests from the investigator often
required the creation of a separate subfile. The Statistical Analysis Syst
(SAS) and the Statistical Program for the Social Sciences (SPSS) were the
statistical packages employed to obtain hundreds of frequency tabulations a
correlational analyses. Work is continuing with an occasional request from
Dr. Weller at Peter Bent Brigham Hospital in Boston.

Analysis of two methods of measuring kidney size. L. Blei, NM, CC. A
statistical analysis was made of kidney data obtained by two different meth
the intravenous pyelogram (IVP) and the bone scan, to determine if the
non-invasive bone scan technique could be used as reliably as IVP data to
predict renal abnormality. LSM assisted in analyzing the variation in
measurement in the two techniques, using repeated measurements of two
observers, leading to the determination that bone scan data is not accurate
enough for the desired purpose.

Copper kinetics in man. E. Jones, DD, NIAMDD. Double-label isotope studi
of copper in normal human subjects are compared with results obtained from
subjects with primary biliary cirrhosis and subjects with Wilson's disease.
LSM is assisting with the modeling effort.

Enzyme levels in epileptic and non-epileptic animals. E. Trams, DMDB, NINC
ATPase levels in epileptic and non-epileptic animals were compared. The
protocol was replicated in several species. Student's t-tests and discrimin
analysis were used.

Snail genetic study. W. Stewart, LEP, NIAMDD. A large data base containing information about an inbred group of snails is being developed. LSM suggested methods for developing computer programs for storage and retrieval of information in this data base, and the display of family trees.

Heterogeneous action of the liver. K. Pang, LCP, NHLBI. Preparations of rat livers are studied, showing that a certain metabolite is eliminated more quickly if it is perfused into the liver than if it is formed there. A mathematical model explaining this effect by heterogeneous action of different regions of the liver is postulated. LSM assisted in setting up this model for curve-fitting to experimental data and production of graphical display output, using MLAB.

Blood factor survival in dogs. R. Jaffe, CP, CC. Fibrinogen and platelet survival is measured in dogs, where the same dogs are subjected to different diets. LSM assisted in revising and maintaining MLAB procedures designed by LSM in the previous fiscal year for this project.

Heart rates on rats given certain drugs. M. Do, CO, NCI. Heart rates were monitored for 8 days on rats given 5 different treatments. Analysis of variance (nested design) was used to analyze this data, graphic displays were produced by MLAB.

Analysis of behavioral data in primates. G. Alexander, BB, NICHD. The effects of prefontal coolings on delayed response performance on three age groups of primates were studied. The study focused on whether the mean percent of error for each group could express the data in the same way as the percent total error/total trials. Statistical procedure used in this study was general linear models (Analysis of Variance). With the aid of the Hewlett Packard 9820, this data was illustrated graphically.

Responses of cyclic AMP-generating-systems in rodent cortex. R. Creveling, LC, NIAMDD. The stimulation of cyclic AMP-generating systems by various neutrotransmitters in mammalian cortical slices was used to characterize the genetic differences between rodent strains. Statistical methods used to determine the extent of this variation and also to make comparisons between the responses to various stimulants and strains were General Linear Models (Analysis of Variance) and Duncan Multiple Range Test. Graphic illustrations were done through the aid of MLAB.

The amphetamine-induced behavioral syndrome in mice. C. Popper, LCS, NIMH. This project involved the study of the behavioral organization of a drug induced psychosis-like syndrome, the changes in behavior of mice in a cage under normal and amphetamine-toxic conditions. A full description of behavioral changes produced by the drug requires that different dose levels of the drug be examined, and that changes which occur through time also be considered. Statistical procedures used in this study were correlations, analysis of variance with repeated measures, and cluster analysis.

Effect of Asbestos fibers on cell growth. M. Wade, NCI. Cell tissue from mice was exposed to variable concentrations of two types of asbestos fibers for variable exposure times. A cell growth model was applied to the cell

counts and a repeated measures analysis of variance was done on the cell growth rate constants. The results show that toxicity increased with concentration and exposure time, and that filtering reduced toxicity.

Brain neurotransmitter activity as a function of enzyme activity.
D. Hoover, E. Muth, LCS, NIMH. Prediction of neurotransmitter activity from level of two enzymes in 60 loci in rat brain. Correlation analysis was used.

Repetition of primary sequence triplets in proteins. H. Saroff, LBC, NIAMDD. Examination of naturally occurring protein sequences shows that appearance of the same triple of amino acids at two or more different places in the chain is a rare event. Randomly generated amino acid sequences with the same composition as the natural sequences have repetitions more often. LSM is currently assisting in analysis of combinatorial probabilities associated with random sequences of amino acids.

Biological molecule similarities. W. Jennings and N. Sharples, LCP, NIAMDD. Physical measurements from calculated minimum energy configurations of nine molecules were obtained. LSM advised on use of C-LAB for analyzing and displaying the similarities between the molecular measurements.

Retinol binding study. M. Lewis, LVR, NEI. Ultracentrifuge techniques are used to study the nature of the binding of retinol to receptor sites in the retina. LSM advised on the use of MLAB to estimate molecular weights and association constants related to retinol binding.

Multiple label scintillation counting. R. Tate, CSL, DCRT and J. Fenstermacher, LCHPH, NCI. New experimental design techniques are studied for the resolution of scintillation counting data with radioactive sources having different energy levels. LSM is contributing to the theoretical analysis.

Measurement of cytochrome oxidation by absorption spectra. R. Hendler, LB, NHLBI. A multi-channel absorption spectrum technique is used to measure the degree of oxidation of several species of cytochrome. LSM assisted in modeling the system, including the characteristics of the spectrophotometer used and background chemical effects.

Modeling the enzyme Fumarase. I. Darvey, PSL, DCRT and L. Kohn, LBP, NIAMDD. Various models of the enzyme Fumarase are compared with currently available data. LSM is assisting in the modeling, including the development of a curve-peeling technique for estimating the coefficients of a rational function used in analyzing initial-rate enzyme data.

Oxygenation of whole blood. R. Winslow, MH, NHLBI. LSM is assisting in modeling efforts concerned with controlling and monitoring of oxygenation of blood.

Oscillating reactions. B. Bunow, LAS, DCRT. Biological reactions are studied which show oscillatory behavior related to the action of selective membranes. LSM assisted in modeling and use of MLAB to study various differential equation systems representing the kinetics of the biological systems.

DNA hybridization modeling. M. Israel, LBV, NIAID. Incorporation of viral DNA into cells is studied by hybridization of labeled DNA. LSM advised on mathematical modeling and estimation of rates using MLAB.

Chemical equilibrium equations for cooperative insulin binding. P. DeMeyts, CE, NIAMDD. A model for cooperative binding was developed and studied theoretically using MLAB. It was used to fit insulin binding data very accurately. LSM assisted in mathematical modeling and use of MLAB.

Predator-prey study. A. Rescigno, LTB, NCI. An ecological model of a pure predator-prey chain is studied. LSM is contributing to the analysis of the transient and equilibrium behavior of the model.

Sample survey on types of nursing care. R. Carlsen, NURS, CC. A 130 item questionnaire was prepared and given to 200+ team and primary nurses in the Clinical Center in a study of job-related levels of satisfaction. The analysis began with factor analysis. In general 4 or 5 factors adequately described the essential 43 variables for both team and primary nurses. Next examined were the differences in job satisfaction for the team vs. primary nurses, using sets of variables as well as the separate variables themselves. After further study probable non-normality of the data suggested two other approaches: multidimensional contingency tables and non-parametric methods. Where satisfaction level differences were found the team nurses were routinely more dissatisfied than the primary nurses. The data was organized by various groupings: age, marital status, educational/training background, years of experience.

Appraisal of personnel rating form 623. T. Gilbert, OPM, NCI. Analysis of new Employee Appraisal and Performance Rating (form 623) and comparison of new form 623 with old form 525. Inquiry as to inconsistency between supervisors, between divisions of NCI. Explore correlation of scores with grade of supervisors. Explore variance of scores within subjects. Correlation, analysis of variance, t-tests are employed.

Quadrivariate normal integral calculation. A. Pratt, DIR, DCRT. A computer program was written to calculate the quadrivariate normal probability distribution function on the IBM 370 system. Adequate accuracy was achieved by using the 10-point Gaussian quadrature algorithm. Quadrivariate normal probabilities were computed for serum electrolytes of a hospital patient population.

NMR spectra. J. Ferretti, PSL, DCRT. A computer package for the calculation of complex exchanged-broadened NMR line shapes was installed on the IBM 370 system, for use with spin systems with symmetry or magnetic equivalence.

Cluster analysis techniques. R. Marimont, IR, NINCDS. LSM collaborated in a study of efficient computer methods for computations of nearest neighbors in multivariate experimental data.

III. PUBLICATIONS

Blum, H. and Nagel, R.: Shape description using weighted symmetric axis features. Proc. IEEE Computer Society Conference on Pattern Recognition and Image Processing, pp. 203-215, Troy, N. Y., June, 1977.

Cheever, A. W.; Kamel, I. A.; Elwi, A. M.; Mosimann, J. E. and Danner, R. N.: Schistosoma Mansoni and S. Haematobium infections in Egypt. II. Quantitative parasitological findings at necropsy. American Journal of Tropical Medicine and Hygiene, 1977, (in press).

Cheever, A. W.; Kamel, I. A.; Elwi, A. M.; Mosimann, J. E. and Danner, R. N.: Schistosoma Mansoni and S. Haematobium infections in Egypt. III. Extra-hepatic pathology. American Journal of Tropical Medicine and Hygiene, 1977 (in press).

Dunham, G.; Pacak, M. and Pratt, A.: Automatic indexing of pathology data. Journal of the American Society for Information Science, 1977 (in press).

Hutchinson, G.: Termination of reactions in chemical systems specified by mass-balance reaction formulas. Math. Biosciences, 33, 213-226, 1977.

Hutchinson, G.: A duality principle for lattices and categories of modules. J. of Pure and Applied Algebra, (in press).

Hutchinson, G. and Czedli, G.: A test for identities satisfied in lattices of submodules. Algebra Universalis, (in press).

Kamel, I. A.; Cheever, A. W.; Elwi, A. M.; Mosimann, J. E. and Danner, R. N.: Schistosoma Mansoni and S. Haematobium infections in Egypt. I. Evaluation of techniques for recovery of worms and eggs at necropsy. American Journal of Tropical Medicine and Hygiene, 1977 (in press).

Knott, G.: A numbering system for binary trees. Comm. of the Asso. for Computing Machinery, 20, 113-115, 1977.

Lutz, R. J.; Galbraith, W. M.; Dedrick, R. L.; Shrager, R. I. and Mellett, L. B.: A model for the kinetics of distribution of actinomycin-D in the beagle dog. J. Pharm. and Exper. Ther, 200, 469-478, 1977.

Nagel, R. and Blum, H.: A symmetric axis basis for object recognition and description. Proc. IEEE Conference on Decision and Control, 168-170, December, 1976.

Rosenblatt, D. E.; Lauter, C. J.; Baird, H. R. and Trams, E. G.: ATPases in animal models of epilepsy. Journal of Molecular Medicine, 2, 137-144, 1977.

Shapiro, M. B.: The choice of reference points in best-match file searching. Comm. Assoc. Computing Machinery, 20, 339-343, 1977.

Shrager, R. I.; Mihalyi, E. and Towne, D.: Proteolytic fragmentation of fibrinogen II. Kinetic modeling of the digestion of human and bovine fibrinogen by plasmin or trypsin. Biochemistry, 15, 5382-5386, 1976.

Winslow, R. M.; Swenberg, M.; Berger, R. L.; Shrager, R. I.; Luzzana, M.; Samaja, M. and Rossi-Bernardi, L.: Oxygen equilibrium curve of normal human blood and its evaluation by Adair's equation. J. Biol. Chem., 252, 2331-2337, 1977.

PERIOD COVERED
July 1, 1976 through September 30, 1977

TITLE OF PROJECT (80 characters or less)

Automated Data Processing of Medical Language

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. G. Pacak	Computer Systems Analyst	LSM DCRT
	A. W. Pratt	Director	DCRT
OTHER:	G. Dunham	Computer Programmer	LSM DCRT
	S. Harper	Computer Programmer	LSM DCRT
	M. DeMeyts-Graitson	Guest Worker	LSM DCRT

COOPERATING UNITS (if any)

Department of Pathology, CC

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Medical Information Science Section

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Work continued on the improvement of the program for information storage and retrieval of pathology data which is being used by the Dept. of Pathology, N.I.H.

The major objective of the project was to develop a generalized system for automated morphosemantic segmentation and interpretation (paraphrasing algorithm) of medical compound words and establishment of formal rules for semantic structuring of medical microglosseries.

Project Description:

In connection with further improvements of the encoder, ICD-O, an up-to-date tumor nomenclature, was incorporated in SNOP. In cooperation with the IBM the encoder was successfully demonstrated at an International Symposium in Upsala, Sweden, in May 1977.

With the cooperation of the Laboratory of Pathology of N.C.I. (Dr. D. E. Henson) work has been continued on the construction of English and French microglossaries for infectious diseases. This includes:

a) construction of a root dictionary for infectious diseases.
b) Morphosemantic analysis of -ITIS compound words.
c) Definition of semantic relations among the semantic constituents of the -ITIS class word forms.
d) The development of a paraphrasing algorithm, which will increase the semantic interpretative power of the lexicon and permit identifications of synonymous phrases occurring in medical context.

The same analysis used for -ITIS forms have been applied to the other high frequency, low ambiguity terminal morpheme classes (-RRHAGIA, -RRHAPHY, -ALGIA, -MALACIA).

Signigicant compression of the lexicon and search time necessary for their recognition has been shown.

In connection with the analysis of medical compound words we have been developing a metalanguage which will permit the identification and classification of connotative and denotative functions of words. This research is important for the development of a theory of the semantic structure of medical dictionaries.

The compiler for the string processing portion of the IRL (Indexed Relation Language) has been brought to a usable state of advanced debugging. It should be a useful tool for small projects while the data base features of IRL are completed.

Dissemination of our major computer based medical lexicons was made to three institutions in the U.S. and Canada.

A report and suggested design for a chemical literature search data base and indexing system were produced for Dr. G. Milne of NALBI.

Future Efforts:

1) Refinement of grammar rules and further development of metalanguage for semantic structuring of medical microglossaries.

2) Further improvements of morphosemantic analysis of English and French medical compound words, and application of paraphrasing rules.

3) Under discussion is the possibility of cooperation with the Institut fur Dokumentation, Information und Statistik, Deutsches Krebsforschungs- zentrum, Heidelberg, W. Germany to develop a compatible encoder for English and German which might be used in connection with the creation of an International Data Bank for Cancers.

Publications:

Dunham, G.; Pacak, M.; Pratt, A.: Automated Indexing of Pathology Data, Journal of the American Society for Information Science, in press 1977.

PERIOD COVERED

July 1, 1976 through Sept. 30, 1977

TITLE OF PROJECT (80 characters or less)

Pattern Recognition

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Shapiro	Research Mathematician	LSM DCRT
OTHER:	C. Herman	Senior Surgeon	LP NCI
	M. Cassidy	Biologist	LP NCI
	D. Symmes	Section Chief	BB CH
	J. Newman	Scientist	BB CH
	A. Lieblick	Scientist	BB CH

COOPERATING UNITS (if any)

Laboratory of Pathology, NCI

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Biomathematics and Computer Science Section

INSTITUTE AND LOCATION

Division of Computer Research and Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS: 2.0	PROFESSIONAL: 2.0	OTHER: 0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Computer pattern recognition methods have been developed for general use and have been applied in two problem areas.
1. Completion of a first version of C-LAB.
C-LAB is an interactive system (patterned after and compatible with MLAB) for handling problems in Cluster Analysis. Users may input and scale data, group data into natural clusters, assess the compactness of clusters, and display and plot clustering diagrams.
2. Pattern recognition of monkey vocalization records.
Vocalization patterns in the form of frequency vs. time data have been recorded for monkeys bred in captivity. Similarities in patterns have been studied.
3. Prediction of presence of cancer from cell sorter data.
Work was begun on the analysis of two dimensional patterns obtained from a fluorescence-activated cell sorter (FACS).

Project Description:

Objectives:

The main objective is to provide an easy-to-use package of pattern recognition programs for the use of NIH researchers and to apply these and similar techniques to particular problem areas.

Methods:

The standard pattern recognition methods plus some of the most recent work has been programmed and applied in a number of problem areas.

Significance to Biomedical Research:

Pattern recognition techniques are now being widely used on biomedical data for classifying objects, finding relationships between variables, and for processing biological images. These applications of artificial intelligence has led to both automatic processing and a better understanding of data.

Proposed Course:

A wider range of pattern recognition and algorithms will continue to be developed and applied.

Publications:

Shapiro, M. B.: The choice of reference points in best-match file searching. Comm. Assoc. Computing Machinery, 20, 5, 1977.

PERIOD COVERED

July 1, 1976 through Sept. 30, 1977

TITLE OF PROJECT (80 characters or less)

Research Topics in Computer Science

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. D. Knott   Computer Specialist   LSM DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Biomathematics and Computer Science Section

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Various storage and retrieval algorithms have been studied. The development of flexible and efficient storage and retrieval algorithms is very useful, since such algorithms are used in almost all computer programs. Thus biomedical computation in particular can benefit from improved storage and retrieval methods.

Currently, an exhaustive survey of storage and retrieval methods is underway. This includes the recently introduced k-d tree method.

Optimal item orderings in split hashing schemes and certain interesting algebraic characterizations of fixed permutation open addressing methods are also being studied currently.

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Project Description:

The object of this project is to develop theoretical bases for new computer methods which will expand and improve the use of computing in biomedical computation. The methods used are the application of known algorithms and the development of new pertinent theorems involving combinatoric and other related mathematics. Research work in storage and retrieval algorithms and their efficiency has been the primary topic of concern.

Currently, an exhaustive survey of storage and retrieval methods is under-way. This includes the recently introduced k-d tree method. Various improvements and refinements in both the algorithms, and their analysis, are being studied.

Optimal item orderings in split hashing schemes and certain interesting algebraic characterizations of fixed permutation open addressing methods are also being studied currently.

Publications:

Knott, Gary D.: "A Numbering System for Binary Trees", CACM, Vol. 20, No. 2, pp. 113-115, 1977.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER
		Z01 CT 00010 LSM

PERIOD COVERED
July 1, 1976 through September 30, 1977

TITLE OF PROJECT (80 characters or less)

Nonlinear Equations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. I. Shrager	Mathematician	LSM DCRT
OTHER:	G. D. Knott	Computer Specialist	LSM DCRT
	E. Hill	Mathematician	LAS DCRT
	J. E. Fletcher	Research Mathematician	LAS DCRT

COOPERATING UNITS (if any)

LAS, DCRT

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER: 0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Methods are developed for solving <u>nonlinear equations</u> frequently encountered at NIH, usually in the context of <u>constrained nonlinear least squares</u> or in the solution to <u>nonlinear differential equations</u>. Related problems, such as <u>asymptotic error analysis</u>, and the efficient treatment of <u>sparse systems</u>, are also considered.

Project Description:

Objectives:

To develop methods for solving nonlinear equations frequently
encountered at NIH.

Methods:

A continuing effort is made to create methods or extend existing methods
to solve problems in a host of NIH applications, and to house those
methods in accessible computer programs or routines. Modelaide and
MLAB are two examples.

Major Findings:

The Levenberg-Marquardt method for non-linear least squares, and the
variant of R.I. Shrager which handles linearly constrained parameters,
have been extended to the L_1 and L_∞ (minimax or Chebyshev) norms.

Least generalized variance experimental design (a method of choosing
the best experimental conditions for resolving unknown parameters) has
been found to produce suspicious results in several cases. An alternate
design criterion is under study.

Papers on both topics have been submitted for publication.

Significance to Biomedical Research:

These methods are now being applied to problems in human metabolism,
cell growth, chemical kinetics, and spectral analysis (UV, IR, CD,
ORD, NMR, ESR).

Proposed Course:

As the methods are proved in test and practice, they will be incorporated
into easy-to-use systems like MLAB, and as a result, the systems them-
selves should evolve to do more useful work with less human and machine
effort.

Publications:

Shrager, R. I.; Mihalyi, E.; Towne, D.: Proteolytic fragmentation of
fibrinogen II. Kinetic modeling of the digestion of human and bovine
fibrinogen by plasmin or trypsin. Biochemistry, 15, 24, 5382-5386, 1976.

Lutz, R. J.; Galbraith, W. M.; Dedrick, R. L.; Shrager, R. I.; Mellett,
L. B.; A model for the kinetics of distribution of actinomycin-D in the
beagle dog. J. Pharm. & Exper. Ther., 200, 3, 469-478, 1977.

Winslow, R. M.; Swenberg, M.; Berger, R. L.; Shrager, R. I.; Luzzana, M.;
Samaja, M.; Rossi-Bernardi, L.: Oxygen equilibrium curve of normal human
blood and its evaluation by Adair's equation. J. Biol. Chem., 252, 7,
2331-2337, April 10, 1977.

PERIOD COVERED

July 1, 1976 through September 30, 1977

TITLE OF PROJECT (80 characters or less)

Discrete Mathematics and Applications

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. A. Hutchinson   Research Mathematician   LSM DCRT
OTHER: G. Czédli   Szeged, Hungary

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Biomathematics and Computer Science Section

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Computer methods for solving an open problem of the theory of vector spaces were revised and improved, specifically concerning lattice word problems for the study of inclusions between subspaces of a vector space.

Project Description:

Objectives:

The project objective is to develop mathematical theory and computational techniques using discrete mathematics (algebra, combinatorics and graph theory), and to apply such methods to appropriate problems of biomedical research and computer science.

Methods Employed and Major Findings:

A biomathematical study during previous fiscal years resulted in a publication during this fiscal year. Linear programming methods were used to study the exhaustion of reactants in chemical reaction systems.

In the previous fiscal year, a computer method was devised and implemented solving an open problem of the theory of vector spaces. It was subsequently discovered that another mathematician, Gábor Czédli of Szeged, Hungary, had independently developed similar methods at about the same time. A joint publication combining these studies was prepared during the fiscal year, and is now in press. A new computer program was prepared and distributed, implementing the improved methods.

Significance to Biomedical Research and the Program of the Division:

General purpose mathematical techniques and computer programs implementing them are made available to the biomedical research community.

Proposed Course:

Work is continuing on theoretical studies to broaden applicability of the computer methods previously developed. New techniques will be implemented on the computer when appropriate.

Publications:

Hutchinson, G.: Termination of reactions in chemical systems specified by mass-balance reaction formulas. Math. Biosciences 33, 213-226, 1977.

Hutchinson, G.: A duality principle for lattices and categories of modules. J. of Pure and Applied Algebra, in press.

Hutchinson, G. and Czédli, G.: A test for identities satisfied in lattices of submodules. Algebra Universalis, in press.

PERIOD COVERED

July 1, 1976 through September 30, 1977

TITLE OF PROJECT (80 characters or less)

Biological and Visual Shape

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. Blum	Res. Gen. Phys. Scientist	LSM DCRT
OTHER:	R. L. Webber	Chief, Clin. Invest. Branch	CIB NIDR
	R. Nagel	Senior Staff Fellow	CIB NIDR

COOPERATING UNITS (if any)

DMG, CIB, NIDR

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Biomathematics and Computer Science Section

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.9	0.9	0.0

CHECK APPROPRIATE BOX(ES)

(a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☒ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project develops and applies a new geometry of biological shape that gives a natural and efficient description to a variety of biological objects at vastly differing levels: chromosomes, cells, organs, organisms.

Applications are to (1) automation of shape analysis for diagnosis and taxonomy, (2) the psychology and neurophysiology of shape processes in vision and (3) the description and understanding of organ and organismic development.

PHS-6040

Project Description:

The overall objective of this project is to develop a formal descriptive
language natural to biological shapes and apply this language to the
variety of problems arising in main areas of biology and medicine:
taxonomy, neurobiology and organismic development. This would permit a
better modeling and understanding of these processes and also allow for
the automation of many shape processes now done by humans.

The methods employed stem primarily from a new geometry based on growth
as the primitive process, and conceived by the principal investigator.
It is applied to a variety of problems, both to clarify the biological
processes taking place and to develop the mathematics in new biologically
relevant directions. These include cell and tissue description from light
microscopy, shape descriptions of developing organisms, chromosome
description, visual psychophysics and visual neurophysiology.

A major accomplishment this year is the completion of a computer program
for performing the necessary geometric processes on 2-dimensional outline
figures and for reconstructing the objects from the new type of description.
These are being applied to cephalometric measurements for the study of
human facial development. There is a collaboration in this work which is
described under project Z01 DE h0158-03 CIA.

A mathematical framework has been developed for extracting these
descriptions for gray scale pictures.

Publications:

Nagel, R. N. and Blum, H.: A Symmetric Axis Basis for Object Recognition
and Description. Proc. of IEEE Meeting on Decision and Control, pp. 168-
170, 1976.

Blum, H. and Nagel, R.: Shape description using weighted symmetric axis
features. Proc. IEEE Computer Society Conference on Pattern Recognition
and Image Processing, pp. 203-215, Troy, N. Y., June, 1977.

PERIOD COVERED

July 1, 1976 through September 30, 1977

TITLE OF PROJECT (80 characters or less)

Multivariate Statistical Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. E. Mosimann	Chief	LSM DCRT
OTHER:	J. D. Malley	Staff Fellow	LSM DCRT
	R. N. Danner	Computer Systems Analyst	LSM DCRT
	C. B. Clark	Computer Systems Analyst	LSM DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Office of the Chief, LSM, DCRT

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS: 1.2	PROFESSIONAL: 1.2	OTHER: 0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☐ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Multivariate statistical methods, (size-shape methods) for analyzing ratios which follow a lognormal distribution have been developed. These size-shape tests have been applied to data on schistosome eggs/organ ratios in man at autopsy as well as morphological data on birds. Computer programs from standard packages SAS, SPSS, have been adapted to give the desired tests.

Project Description:

The overall objective of this project is the study of multivariate
statistical methods for the analysis of data which take the form of ratios
or proportions. During this past year there was continued development of
statistical tests and study of data including the distribution of
schistosome eggs by organ at autopsy, data of A. Cheever, NIAID, and
morphological measurements of birds, F. James, NSF. As a result of work
reported under this project last year (Project Z01 CT 00013-02) Mosimann
visited the Commonwealth Scientific and Industrial Research Organization,
CSIRO, of Australia, under their international visitors program in
mathematical statistics, and gave lectures based on this work in five
major Australian cities.

Publications: None

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities   1. <u>DCRT</u>

2. <u>COMPUTER SYSTEMS LABORATORY</u>   3. <u>Alan M. Demmerle</u>
                                                    Chief

I. SUMMARY

Function

The Computer Systems Laboratory (CSL) identifies and solves problems in
areas of biomedical research and clinical care where real-time data collec-
tion, analysis, display and experiment control are required, where economic
considerations favor a small computer or where proximity of the computing
equipment to the work site is important to successful solution.

The activities of CSL's electronic engineers and computer scientists center
in these principal areas: computer applications in a clinical environment,
computer applications in laboratory research, and consultation with research-
ers in need of computer expertise.

CSL's method of approaching each project varies as each problem presents
unique challenges. Sometimes the objectives of a project are clearly
defined. The investigator knows exactly what he wants automation to achieve.
In this case the path to solution of the problem is conceptually straight
forward, even though it is often time consuming and technically difficult.
In projects of this kind, CSL staff analyze the user's specific requirements,
evaluate various alternative solutions with regard to technical merit, time
to completion, and cost. The hardware and software aspects of the system
which best meet the user's needs are then specified.

A different approach is required when an investigator believes his research
might benefit from automation but does not know exactly how to take advantage
of the possibilities. In projects of this kind, members of CSL become more
involved with the research in order to discover how automation can be
achieved and how research methods need to be altered to utilize this
technology.

When components that meet the user's needs are not commercially available,
they are developed by the CSL engineering and programming staff and are
combined with those system elements that are commercially available. The
system is refined to the point where it becomes a functioning, integrated
part of the user's research. Since users' requirements often change as their
research progresses, collaboration between the users and CSL staff continues
beyond the initial implementation of the system so that necessary adaptations
can be made.

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Over the past ten years CSL has worked with nearly all the NIH Institutes on a wide variety of projects. Some have been quickly concluded. Others have required several years from the initial functional analysis through design, development, installation, and continuing collaboration with users to adapt the systems as research requirements evolve.

Scope of Work

This year CSL's 33 person staff worked on approximately two dozen projects. The bulk of this work has been directed toward our principal mission--the support of intramural research, but we have done a significant amount of consultation for extramural programs, and a little work for government groups outside NIH.

Highlights of the Year's Activities

CSL involvement in developing small-computer support for clinical care and laboratory research programs continued during FY 77. Minicomputers, micro-computers and small programmable calculators have all been used. Use of the central DCRT PDP-10 computer to support these small computers has grown. This represents the maturing of a concept toward which DCRT has been working for some time: an interactive computer network in which the versatility and usefulness of small computers in laboratories are expanded through direct connection with the computing power of a large central facility. CSL anticipates that wider use of this approach will provide an economical computer capability for on-line laboratory process control and data acquisition and better long-term data storage and retrieval capability.

In its consultancy role, CSL continued its work with intramural programs and expanded its services to staff in NIH collaborative and extramural programs. Intramural consultation often included development of hardware and software systems. Extramural consultation activities are primarily advisory in the areas of automated data collection, display and analysis, data transmission, certain aspects of biomedical sensor design and all aspects of real-time computer design.

Our work seems to cluster in two areas of computer technology. The first cluster includes projects which represent large investments of manpower and are characterized by (a) a requirement of a highly complex task for which new algorithms must be developed and (b) a large assortment of complex instruments interacting with each other. One example of this class is the Radiation Therapy project which involves a large spectrum of activities, including the development of algorithms for pattern recognition of tomographic images. A second cluster seems to be developing around projects requiring a much smaller investment of manpower and capital, an area of work which to some extent is the result of the emerging microprocessor technology. This cluster is characterized by relatively small, yet sophisticated, requirements for limited on-site computing power. One example is the scintillation counter data logger. Prior to the microprocessor technology, this type of sophisticated automation was not economically feasible on such a small scale, and so a class of laboratory automation problems was neglected. Of course, there remain some projects in CSL which lie between these clusters.

Microprocessors are also making a significant impact in the design of laboratory instruments. Some of the newer versions of large, commercially available instruments (e.g., spectrophotometers) now include a microprocessor for the formatting of data and for some control functions. Custom made instruments, such as are made in other groups within NIH, have also reached new heights of sophistication as a result of the microprocessor, an important new element of the computer technology.

Future Plans

To continue its present range of activities and respond to these new challenges, CSL plans to maintain a staff which has both a proven breadth of experience and competence in system development and expertise in new digital equipment and techniques.

Reductions in staff at the end of this reporting year will influence our productivity. These reductions may result in our need to find a more rigid and formal system with which to choose the projects on which we work and to set our priorities for assigning our manpower to them.

LEVEL OF EFFORT AND CAPITAL EXPENDITURE BY MAJOR PROJECT (July 1976 - September 1977)

Project Name	Project Leader	Effort (Man Year)	DCRT Capital Invested (K$)
Radiation Therapy, NCI, RO	Syed	7 1/2	15
Intensive Care Unit, NHLBI, IR, SU	Syed	6 3/4	38
Medical Intensive Care Unit, CC	Syed	1	0
S-T Segment Mapping, NHLBI, IR, CB	Plexico	3/4	20
Cell Sorters, NCI	Schultz	1 1/2	4
Hybrid Replacement	Plexico	1 1/2	30
Scintillation Counter Data Logger	Plexico	1 1/2	12
Pulmonary Function, NHLBI	Plexico	3/4	0
Potentiometric Titration Controller, NHLBI, IR, LC	Plexico	3/4	0
Cardiac Scintillation Probe, NHLBI, IR, CB; and CC, NM	Schultz	1	3
Automated ECG Processing, CC	Plexico	3/4	0
Medical Telecommunications	Plexico	3/4	2
Computer Communications	Plexico	3/4	0
Intramural Laboratory Support	Schultz	3	0
Cardiovascular Signal Analysis, NHLBI, IR, SU	Schultz	1	0
Mass Spectrometer, NIMH, LCS	Schultz	4	5
Distributed Data Acquisition and Control System, NIAMDD	Schultz	2	8
Computers in Cardiology Conference	Ostrow	1/2	2
Agricultural Research Center, USDA	Plexico	3/4	0
Grants Voting Machine, NHLBI and DRG	Schultz	1 1/4	10
Consulting - Extramural Programs	Demmerle	1	0

Radiation Therapy, NCI, RO

CSL, in collaboration with the Radiation Oncology Branch, NCI is developing a computer system to utilize the detailed anatomic and density information available from computer assisted tomography to improve radiation treatment planning. Our system allows the radiotherapist to review scans of the tumor area at a video terminal, vary the gray-level spectrum to emphasize a particular structure, or zoom on an interesting feature. Once satisfied with the detail presented, individual anatomic and tumor contours may be outlined manually with an electronic pen, or automatically under computer control. The contours and a tentative set of therapeutic energies selected by the physician are processed through algorithms (Atomic Energy of Canada treatment planning software) that determine dose distributions at and around the tumor. The computer can then be instructed to draw the resulting treatment plans, as well as life-sized representations of the scan.

The computer was recently installed in the clinical environment, after eight months of development in our laboratory. Following a final checkout of the system, further development, to expand to a multi-user configuration, is expected. Research into treatment optimization and studies of the feasibility of computer-controlled therapy machines has begun.

Intensive Care Unit, NHLBI, IR, SU

The system developed over the last five years for the Surgery Branch, NHLBI provides continuous monitoring of ECG, arterial pressure, venous pressure, temperature, blood loss, and urine output, simultaneously from four beds. During FY 77 the computer monitored some 150 patients during their stay in intensive care. CSL added a security protocol, limiting access to the data base from certain terminals, provided the capability to move patients and their data from bed to bed within the computer, added a five-minute storage of the ECG at every bed, and improved the on-line computation of cardiac output. Capacity was extended from five terminals to ten, a preliminary user's guide was written, and an extensive technical manual was completed. CSL designed and fabricated hardware preprocessors, which detect significant features of the ECG and arterial pressure waveforms (R-wave, upstroke, notch, etc.), have been installed in the computer and will become operational upon completion of the computer software to interface them to the system. We also completed a nurse's station that includes workspace, desk, and computer console. Paper copy of any graph or chart is now available at the bedside or at the nursing station.

Intensive Care Unit Support, NCI

CSL has worked with the Surgery Branch of NCI to develop computer-aided monitoring for two operating rooms and the NCI postsurgical recovery room in the Clinical Center, with emphasis on respiratory monitoring, and has generated a Request for Proposals to satisfy those requirements.

A recent decision by the NIH Clinical Center administration to create an independent medical intensive care unit led to a new combined Request for Proposals for both units with automated monitoring and respiratory analysis in the new unit. Therefore, progress on this project is reported under the heading Medical Intensive Care Unit Support, CC.

Medical Intensive Care Unit Support, CC

CSL is working with the Clinical Center staff to provide computer-aided monitoring facilities to a newly organized medical intensive care unit. There will be strong emphasis on respiratory monitoring and intravascular studies in order to evaluate pulmonary function. Computerization of intensive care units provides many advantages, including rapid display of trends, alarms when vital signs deviate from predetermined limits, immediate computation of acid-base balance and cardiac output reporting and logging mechanisms which relieve nursing staff of clerical functions, and establishment of a manageable data base for current and future research. However, the requirement for pulmonary function evaluation is the primary impetus for a computer in the Clinical Center medical ICU.

CSL also studied the computer requirements for a postsurgical recovery room in the Surgery Branch, NCI. These requirements are sufficiently similar to those of the medical ICU that a comprehensive plan for both units is justified. Although computer-aided monitoring is not being considered now for the NCI unit, selection of compatible medical electronics will ensure that future connection to the medical ICU computer will be possible.

During the past four months, in conjunction with the Clinical Center staff and NCI surgeons, CSL has generated a Request for Proposals for appropriate equipment. This system includes computer-aided patient monitoring and a mass spectrometer for the medical intensive care unit, and new bedside medical electronics for both the medical ICU and the NCI surgical care room. Equipment installation is planned for the spring 1978. Since no commercially available systems offer the required respiratory monitoring functions, CSL will undertake modifications of the purchased software and will interface the medical mass spectrometer to the computer system.

S-T Segment Mapping, NHLBI, IR, CB

The Cardiology Branch, NHLBI is interested in studying the effects of drug therapy (e.g., nitroglycerin) on acute myocardial infarction patients as measured by changes in the elevation/depression of ECG S-T segments. CSL has developed algorithms which permit these ECG measurements to be made automatically and has determined that the measurements can be made using a microcomputer. A prototype system configured around a microcomputer and capable of taking measurements from 35 simultaneous ECG leads is being constructed. When completed and evaluated, a determination will be made as to whether 35 simultaneous leads are necessary for accurate measurements as compared to sequentially using several lead groups each containing a smaller number of leads.

Cell Sorters, NCI,

A project started several years ago to provide data capture and analysis for two different types of cell separators located in the National Cancer Institute was completed this year. Presently both the FACS II, the sorter belonging to the Immunology Branch, and the LASL, the cell separator belonging to the Laboratory of Pathology, share an 11/40 computer system physically located in the same laboratory as the FACS II. The LASL sorter is located several hundred feet away but still connected by cable to the 11/40. Recently FACS I was replaced by FACS II which provided an additional fluorescence channel for characterizing cells. An already heavy data capture and data analysis schedule would have been further limited if the capability for utilizing the additional FACS II parameter were added to the data acquisition program. Therefore CSL has recommended purchase of a second computer system compatible with the existing system and dedicating one computer for data analysis and processing for each cell separator. Further requirements for both data analysis and computer controlled sorting have been established by NCI so that next year we will probably begin a new phase of development on this project.

Hybrid Replacement

In late 1974 NIH management determined that the space occupied by DCRT's Hybrid Computer System on the eleventh floor of Building 10 would have to be relinquished in favor of other research programs. CSL undertook the task of developing a system which would replace the functions of the Hybrid System, but would require substantially less space. All essential functions of the Hybrid Computer were replaced by the end of FY 76; the addition of new functions and refinements continued through the TQ and the first half of FY 77. The system is now a fairly elaborate resource for analog to digital conversion and various forms of graphic output and display. Since work to replace the Hybrid Computer is complete, this project will not be reported again in future years. However, the new system will continue to be used by those investigators who formerly used the Hybrid and by CSL staff as a test bed for operating systems and communication software and for real-time software development for other PDP-11's here at NIH.

Scintillation Counter Data Logger

The need has long existed for a device to record the output of liquid scintillation counters and similar instruments on low cost computer compatible media other than punched paper tape, in many ways a very inconvenient, and considered by some an obsolete medium. CSL has developed a data logger which accepts scintillation counter data and records it on ANSI standard digital cassette tape. Data from the tape may subsequently be transmitted for processing to DCRT's DECsystem 10 or IBM 370 via a terminal equipped with a compatible cassette unit. The data logger is microprocessor controlled and therefore may be adapted to a variety of instrument characteristics by simply replacing a program contained in a programmable read only memory. Three data loggers have been fabricated and are being field tested by scintillation counter users. Assuming they prove acceptable, CSL will look for an administrative mechanism by which multiple units can be manufactured and distributed to users of scintillation counters who require computer processing of their data.

Pulmonary Function, NHLBI

The Pulmonary Branch, NHLBI utilizes automated pulmonary screening apparatus in performing its own research tasks and in fulfilling its mission as a pulmonary function service laboratory for NIH. A data base management scheme for the storage and retrieval of test results was deemed necessary. A system to perform this task was jointly undertaken by CSL and DMB of DCRT and was completed during March 1977. The system involves temporary storage of results on a minicomputer in the Pulmonary Laboratory followed by transmission of results via telephone line to DCRT's IBM 370 central facility, where they are available on an interactive basis using a terminal.

Potentiometric Titration Controller, NHLBI, IR, LC

This effort involves a new approach to potentiometry in which microcomputer controlled pulses of electric current replace incremental additions of chemical oxidants and reductants. Most developmental work, including the microcomputer system, the various interfaces to laboratory instrumentation, and software for controlling potentiometric titrations, was completed by the fall of 1976. The system has now been in routine experimental use for nearly one year.

Cardiac Scintillation Probe, NHLBI, IR, CB; and CC, NM

A microcomputer based, non-imaging, scintillation probe system has been developed to allow continuous, non-invasive monitoring of left ventricular function. The microcomputer and electronics are mounted on a cart and can be easily positioned at the bedside. The system is programmed such that during consecutive three minute intervals, it automatically (1) acquires scintillation data from the probe, (2) organizes the data into a composite left ventricular time-activity curve, (3) permits the curve to be constructed only from heartbeats having a user-selected range of lengths, (4) corrects the curve for left ventricular background, (5) calculates ejection fraction from the curve, and (6) displays the curve and all calculated values of ejection fraction as a function of time from the onset of monitoring.

This system is presently undergoing clinical evaluation.

Automated ECG Processing, CC

The Clinical Center, ECG Laboratory has indicated a need for faster turnaround for ECG processing than is possible using the current system of digitization by the DCRT MAC-16 minicomputer followed by processing on the IBM 370. There is also concern that LAS, DCRT will not be able to support the digitization phase on an indefinite basis. As a result, CSL, in collaboration with LAS, undertook an evaluation of alternative methods of obtaining routine computer processing of ECG s. It was concluded that the purchase of a turn-key minicomputer system is the most cost-effective way of meeting Clinical Center requirements. Clinical Center management, while apparently concurring with the recommendation, indicated that funds for such a system were not available at present.

Medical Telecommunications

CSL has long had an interest in the development of technology by which computerized medical information can be made available using a touchtone telephone as a computer terminal. To this end a microprocessor controlled voice synthesis system which converts computer coded text to spoken English has been developed. Efforts on this project were set aside in favor of othe priorities for the TQ and much of FY 77. However, work has recently resumed and a completed prototype should be available by the fall of 1977.

Computer Communications

It is often necessary to be able to transfer information between laboratory minicomputers and a large computer system such as the DECsystem-1(in order to exploit the large system's data analysis and software developmen facilities. To meet this need, a software package called "CLINK" (Communica tions LINK) has been developed jointly by CSL and CCB. CLINK enables communications between DEC PDP-11 s (the most commonly used minicomputer at NIH) and the DECsystem-10.

CLINK provides the following capabilities:

1. Terminals physically connected to a PDP-11 which is, in turn, connected to the DECsystem-10 can operate as "virtual terminals;" i.e., the terminal appears to be a normal terminal connected directly to the DECsystem-10 and can be used to perform all the usual time-sharing functions.

2. Data files can be transferred from the PDP-11 to the DECsystem-10.

3. Data files can be transferred from the DECsystem-10 to the PDP-11.

Currently, CLINK software has been written for the DECsystem-10 and for PDP-11 s running the RSX-11M or RT-11 F/B operating systems. An experimenta version of CLINK is in use on six PDP-11 s at NIH. Future plans are to solve the remaining problems with the current implementation and to produce compre hensive documentation.

Intramural Laboratory Support

Support for intramural research laboratories through the development of specialized computer systems and data acquisition and control systems has long occupied a significant portion of CSL resources. The current year represents a continuation of this trend. Many projects in this category require the investment of substantial manpower and resources and are there-fore reported separately. Those which can be accommodated by efforts rangin in duration from a few hours to a few weeks have not been reported separatel The nature of these projects usually involves an extension or a variation in the application of an existing computer or data acquisition system and, mor rarely, the development of a new system. Assistance provided by CSL is normally in the form of technical advice and consultation but may include th development of software or a new hardware interface to an instrument. Durin FY 77, assistance was provided to laboratories in a number of Institutes, including NIAID, NEI, NIEHS, as well as NIMH.

Cardiovascular Signal Analysis, NHLBI, IR, SU

During the past year programs have been developed to assist researchers in analyzing physiological signals collected during experimental surgery on dogs. These signals, primarily hemodynamic in nature, are recorded on analog tape during the laboratory experiment. The tapes are later taken to the computer (the Hybrid replacement, a PDP-11/40) where the signals are reproduced and digitized. Laboratory data thus digitized is stored on digital tape in physiologic units (rather than A/D converter units) in a format convenient for the analysis programs. The analysis program provides beat-to-beat processing of the data and calculates parameters to assist in the study of left ventricular function. This project will provide a protocol for routinely determining LV function in dogs in support of future cardiovascular research studies. Once an acceptable protocol is established, programs to implement it will be designed such that the researcher can control and run the programs himself through extensive prompting on a terminal.

Mass Spectrometer, NIMH, LCS

In collaboration with Dr. Markey, NIMH, a project to automate ion focusing and data acquisition from an LKB 9000 mass spectrometer was started in FY 77. Ion focusing is accomplished using a PDP-11/10 computer to control the accelerating voltage of the spectrometer. Although data acquisition and control are essential, the compelling reason for developing this system was to allow a user to create and use his own data manipulation routines, a feature not present on commercially available mass spectrometer data systems. Unique hardware required for the LKB 9000 - PDP-11/10 interface is now installed and functioning. The principal hardware elements are an accelerating voltage power supply (0-10v supply input, 3K-4Kv output), a high resolution analog to digital converter, and a digital interface to the mass marker readout.

Software has been divided into four separable phases for development and use; initialization, calibration, data acquisition, and data analysis. The first two phases are completed. Data acquisition and analysis are essentially complete but require testing and probably modification based on experience during testing. Embellishments to the entire system based on results obtained from use in the laboratory will occur later this summer. Hardware documentation is complete. Software documentation will be postponed until the system is acceptable for routine laboratory use.

Distributed Data Acquisition and Control System, NIAMDD

A prototype Distributed Laboratory Data Acquisition and Control System is being implemented for NIAMDD in Building 2 as an eventual replacement to the Laboratory Computer System developed here in CSL for Building 2 several years ago and which has now become overloaded. The new system will consist of a network of remote microprocessors connected in a star configuration through a communications microprocessor to the existing Honeywell 516 (H-516) computer. Laboratory data will be collected locally in real time and transmitted at a convenient time to the communications processor. A standard communications protocol (DECNET) will be used for this data transfer. After the data file has been correctly received by the

communication processor, it is put on a queue, located on a disc attached to the communications processor for processing in the H-516. When the H-516 becomes available, this queue of data files is transferred to the H-516.

A working prototype of the communication processor is now installed in Building 2 and work is progressing on the link to the H-516. After the network is functioning, the tie to the first instrument, a Cary 118 spectro-photometer, will be started.

(This activity grew out of what last year was reported under two projects, Shared Laboratory System, NIAMDD and Distributed Microcomputer Prototype.)

Computers in Cardiology Conference

CSL has continued its support of the annual International Conference on Computers in Cardiology. The Conference provides a forum for direct inter-action and exchange between physicians, computer scientists, and engineers who are involved in various aspects of clinical systems in the field of cardiology. CSL helped organize the 1976 Conference at Washington University in St. Louis, Missouri, and edit the Conference Proceedings. We are also involved, though to a lesser degree, in the planning of the 1977 Conference which is to take place in The Netherlands.

Agricultural Research Center, USDA

In July of 1976, the Agricultural Research Center (ARC) at Beltsville, Maryland, requested that CSL perform a study and analysis of the data acquisition and processing needs of its Nutrient Composition Laboratory (NCL). This interagency request was initiated as a result of CSL's reputation in Laboratory Automation. Two senior staff members of CSL were assigned to the study and began work on it in October, 1976. A detailed analysis of the needs of NCL was performed and, as a result, a recommendation for the implementation of a distributed data acquisition and processing system was made. The final report to NCL, submitted in February of 1977, was all inclusive. It not only presented a technical approach, but addressed the required levels of funding and manpower as well. The most recent information available to CSL is that the Nutrient Composition Laboratory plans to imple-ment the CSL recommendations, using existing ARC resources.

Grants Voting Machine, NHLBI and DRG

CSL was asked by the Director, Division of Extramural Affairs, NHLBI to develop an electronic voting machine for use in study section meetings. The purpose of the device is to record individual priority scores on grant applications and provide the Executive Secretary with instantaneous informa-tion concerning number of individuals voting, the average score, high and low votes, etc. A prototype system consisting of thirty individual voting terminals and a master control and display station was designed and fabricated. It was demonstrated to senior staff of DEA, NHLBI and DRG in June, 1977. The voting system will be used in a number of study section meetings through the summer and fall of 1977. Extramural staff will make a determination of its utility and, if it is found useful, provide CSL with recommendations for improvements to be incorporated into a future model.

Consulting - Extramural Programs

The past year has seen an increasing demand for CSL expertise by extramural programs and, to a lesser extent, by other agencies. A typical example dealt with the rapidly escalating costs for computing encountered by NHLBI's Multiple Risk Factor Intervention Trial (MRFIT). Following an assessment of data processing methods employed by the MRFIT Coordinating Center, recommendations on how to stabilize future costs were made.

While most activities in the area of extramural consulting have been computer related, there has also been a significant requirement that CSL provide consultation in other areas of engineering. For example, consulting support has been provided to the FDA with regard to the development of an electromagnetic compatibility standard for hospital environments.

In addition to the above, consulting assistance has been provided to the NIAMDD Artificial Kidney Program, the NICHHD Pregnancy and Infancy Branch, the NCI Carcinogen Bioassay and Program Resources Branch, and to the Armed Forces Radiobiological Institute.

III. Publications and Presentations

Ader, R., Lepley, A., Songco, D., Becker, E.: Microprocessor/Based Control and Data Acquisition System for Spinlock Pulsed Spectrometer. Poster Session at 18th Experimental NMR Conference, April 1977.

Gorlen, K., Ricart, G.: CLINK--An Asynchronous File Transfer Program. Digital Equipment Corporation User's Society, December 1976.

Hendler, R., Songco, D., Clem, T.: Automated Electrodic Potentiometry. Analytical Chemistry (in press).

Holsinger, W., Kempner, K.M.: An EKG Telephone Transmission System with Reverse Channel Capability. IEEE Transactions on Biomedical Engineering (in press).

Kempner, K.M.: The Continuous Monitoring of Cardiac Arrhythmias. Proceedings of the 1976 IEEE International Conference on Cybernetics and Society. November 1976, pp. 214-218.

Kirkland, L., Syed, D., Risso, W., Morgan, T., Smith, L.: The Role of CT Scanners in Radiotherapy. Proceedings of Society of Photo-Optical Instrumentation Engineers, September 1976.

Lee, H.: Boundary Detection in Computer Tomographic Images. 30th Annual Conference Engineering in Medicine and Biology, November 1977.

Ostrow, H.G., Allen, S.I., Bacharach, S.L., Green, M.V., Borer, J.S.: A Portable Scintillation Device for Monitoring Left Ventricular Function. American Heart Association (TALK) November 1977 (abstract published).

Tate, R., Barden, L., Schultz, A.: Selected Ion Recording Minicomputer Data System for Magnetic Deflection Mass Spectrometers. Poster Session Presentation at the 25th Annual Conference on Mass Spectrometry and Allied Topics, May 29-June 3, 1977.

July 1, 1976 through September 30, 1977

NATIONAL INSTITUTES OF HEALTH

Division of Computer Research and Technology

Summary of Branch Activities   1.   DCRT

2.   DATA MANAGEMENT BRANCH   3.   J. Emmett Ward
                                           Branch Chief

I.   SUMMARY

Mission and Function

The Data Management Branch (DMB)   provides   advice
and   assistance   to research investigators, program
officials and administrators throughout NIH in   planning
for   and   obtaining   computer data processing services.
In this role the   branch is   a   central   NIH   resource
for computer systems analysis, design and programming.

Scope of Activities

DMB   staff   designs   and   creates   computer-based   data
management systems for specific users and   trains   those
users.   They   also   teach   courses   about   some   data
management and programming tools, provide advice on data
management techniques   to   NIH programmers   and   serve
as   consultants   on   computer based systems proposed by
other NIH groups for   implementation   by contractors.
Finally,   DMB   creates   and maintains general purpose,
user-oriented programming tools to   speed   building   and
improve operation of specific applications systems.

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Design Philosophy

Many computer applications are straightforward.
Others involve an extended period of exploration to
define the users' needs, the appropriate
information processing techniques and the computer
methods best suited to the users circumstances.
Clients pay for DMB work under the NIH service and
supply fund as well as for running the completed
systems in the NIH Computer Center. Therefore, the
DMB approach to projects can best be described as
conservative but progressive, using, when possible,
existing programming tools to minimize development time
and costs and to maximize system reliability and ease of
maintenance.

The branch develops most systems for operation by
the requesting organization. This places control
of the completed computer application in the hands of
the user, assures each user operational
independence from DMB and frees the branch to work on
new projects.

Experience shows that large complex projects, involving
many users, may flounder for organizational and
sociological reasons, as often as for technical reasons.
Fortunately special attention to planning, training the
users, and care in implementation of the system can
avoid many of the difficulties.

1976 Highlights

In FY77 DMB again worked on more than one hundred
projects involving virtually every Bureau, Institute and
Division of the NIH. Over 35% were projects for
in-patient care, clinical research, or epidemiology;
more than 15% for laboratory research areas; almost 35%
for program direction, management and administration;
approximately 10% for biomedical communications and 5%
for development of data processing and analytic tools.
About 35% of the projects required less than 80 hours
each of DMB work and another 35% less than 600 hours
each. The project list in Section II gives a view of
the breadth of the DMB work. The following items
highlight a few areas of particular interest:

<u>The Clinical Information Utility (CIU)</u> represents the largest single DMB effort, approximately 3 man-years. It is a joint project between the DMB Clinical Support Section and the Office of Clinical and Management Systems in the NIH Clinical Center to develop a powerful retrieval capability for NIH scientists.

The project began about four years ago with the vast files of data generated by the clinical laboratories in the Clinical Center, about 1.2 million chemical, hematological and microbiological tests per year. Because of this volume the NIH Clinical Laboratories pioneered the use of computers in the 1960s to automate laboratory tests and to record and report daily results. Storing years of data was a task beyond a computer system designed to support laboratory operations. The CIU system receives data from the clinical lab computer system, archives it in the NIH Computer Center and retrieves specific subsets on request.

During FY77, a new method for retrieving patient data on criteria other than patient registry number was developed. The most significant problem with the CIU is that it is constantly growing both horizontally with respect to the number of data elements collected on each patient and vertically by the simple addition of new patients. Prior to this year, retrieval of information has been based either on serial searching or on using inverted list and hierarchical structures. The new method for controlling retrievals creates a patient experience profile for each patient.

This profile can be easily and inexpensively accessed to obtain information on the number of patients who might satisfy a particular set of search criteria and can be further keyed to access the specific patient information directly. A relatively short bit pattern of profile conditions on a set of patients numbering in the thousands can represent billions of bytes of actual stored information. Retrieval costs, which previously could be unpredictable, are now running in the $2.00 to $15.00 range per retrieval, based on complexity of search and number of records selected.

Using an innovative approach, DMB has reduced the cost of updating this CIU data base by over 50% in FY77. Ten thousand transactions can now be processed for $1.75. It is believed that these breakthroughs which have been accomplished in the face of continuous CIU growth, are flexible enough to sustain significant savings and a relatively constant cost through many more years of expansion.

The Cardiac Valve Replacement Study for the Surgery Branch, NHLBI, entered a new stage of simply updating the file with new patient information. The need became apparent for a comprehensive retrieval system for surgical planning to make informed decisions in the light of previous experience. The DMB applications programmer on the project joined forces with the Software Support group to implement the Symbolic Logic Retrieval system. The system interactively accepts free form specifications of the user's file structure and generates a customized program, which in turn interactively retrieves selected records from the user's file. The system used the powerful DMB programming tool, RMAG22, to analyze the logic of the user's request, convert it to canonical form and generate the necessary program in standard COBOL Language. The general nature of this approach proved adaptable to several other systems.

The Patient Record System for the Cardiology Branch, NHLBI, was a new project undertaken this year. The purpose of the system is to establish, maintain and provide patient data. It will include information from Admissions, Physical Examination, EKG, etc. The system is still in early stages of development.

Adriamycin Toxicity Study
Adriamycin therapy in cancer treatment seems to increase the risk of congestive heart failure. Many factors such as dose level, length of treatment and concomitant therapy must be analyzed to determine whether this suspected relationship is real. In support of this analysis by the Cancer Therapy Evaluation Program, NCI, DMB has designed forms and developed the software to collect data on approximately four thousand patients who are being treated with adriamycin in ten national geographic regions. Analysis of these data is now beginning and will be compared to anticipated European data as it is collected.

The Mutagenesis Bioassay Testing System for the National
Institute of Environmental Health Sciences is an
interactive system, which is intended to standardize the
day-to-day laboratory functions for mutagenesis
experiments. Utilizing a basic instructional outline
and the variable data endemic to each experiment the
system (1) will interact with the laboratory technician,
(2) accept and check his input, (3) analyze results of
critical events, and (4) provide guidance for further
steps as each experiment progresses. The software for
the initial phase of this effort is complete and a
contract award for a specific set of mutagenesis
experiments utilizing this computer system has been let.
This contract should provide meaningful information
concerning the efficacy of this approach.

The Division of Extramural Affairs supports the NHLBI
Program of biomedical research, which includes research
grants, research manpower grants, and research
contracts. This fiscal and programmatic information
comes partially from the IMPAC system of the Division of
Research Grants and partially from data captured and
entered by Reports and Evaluation Branch (R&EB),
NHLBI. The DMB was called upon to help them survey
their present system and to upgrade it.

The project included documentation of the current
system - paper flow, computer system flow
including human interfaces, computer programs, data base
descriptions; upgrading of the Abstract file update and
retrieval facilities; establishment and full
documentation of a Trainee File with its update and edit
facilities; upgrading of the Master File, with special
attention to purification of the data. Suggestions for
improvement of paper flow as well as data capture and
report streamlining were implemented. Completion of
this project should aid R&EB personnel in meeting their
current and end-of-fiscal-year requirements more easily.

The Reproduction Research Branch of NICHD is involved in
the preparation of purified proteins (hemoglobin,
albumin, hormones) by gel electrophoresis. Using
a scanning isoelectric focusing assembly (Catsimpoolis
Apparatus) it is possible to obtain, across time,
quantitative data on the position, bandwidth, peaks,
etc. of the protein as it filters through the gel.
These data, when analyzed, can provide information
which enables researchers to determine rules
controlling the behavior of the proteins in the gel and
to refine their purification procedures.

Working closely with the research scientist, DMB staff is developing, in a quasi-heuristic manner, a portable, interactive system which can interface with a non-computer oriented user for performing the statistical analysis and for displaying peaks.

Molecular Hematology Branch, NHLBI, is studying 20-25 sickle cell anemia patients who have entered NIH over the last 2-2 1/2 years. They are gathering information on the clinical course of the disease in order to predict the course in individual patients. There is great variance among patients and it has been difficult to evaluate treatments. DMB is designing a data entry and retrieval system from which a patient history can be printed as patients reenter the hospital, and on which correlations can be run. Additional tests will be added to the data base as they seem relevant. The system involves use of the DMB Unified Generators to create and update files and retrieve and report information from those files for analysis.

Future Plans

In FY78 and the foreseeable future, DMB will pursue the same direction that has proven successful over the last few years. There is still a clear need for a central NIH resource for advice, consultation, systems analysis, design and programming on data management applications of computers. The DMB staff has accumulated a wealth of experience in developing NIH data management applications on the NIH Computer Center systems. It has a reputation for reliable, effective work. It has a powerful set of tools to generate new applications and works with experts in other DCRT laboratories when more complex statistical/mathematical analyses and/or engineering skills are required to satisfy a specific need.

DMB projects will continue to arise from the data processing needs of NIH, a remarkable mix in size and substance. The best solution/system for a given problem/project will, of course, depend on the technology available at the time it is undertaken. The prospect of "intelligent" terminals, as well as more powerful software, means only that more options will be available, not that a given user will get a more complicated or expensive solution/system. Nevertheless, some data processing needs at NIH will undoubtedly lead to more ambitious projects.

The Clinical Center is in its second year of installing the Technicon Medical Information System. This proprietary system receives and transmits medical orders and reports of test results and some treatment actions in support of medical care.

In the Clinical Information Utility (CIU) area, DMB provides an archival methodology designed around the idea of integrating medical data files and making them easily retrievable. Much still remains to be done in the integration area due to the volume and mix of the data being archived. Methods are also being developed as part of the integration effort to assure that retrieval of the data will be facilitated. Retrieval of patient information which matches any logical criteria relevant to any of the data currently collected is a reality today. As new data are collected software can easily be adopted to provide new retrieval capabilities.

In addition to the above, the CIU also has the ability to hold subsets of the data retrieved for further analysis. This approach allows the research investigator to receive today's information in the form of a sub-file for more detailed analysis and to have this sub-file updated as new information becomes available.

For readmitted patients, DMB is planning to provide a microfiche summary of all information collected during previous admissions. This summary adds to the information base that the research investigator currently has and will hopefully enable him to begin new treatments and examinations in the light of a more comprehensive review of previous experience.

With all of these retrospective capabilities available, one question still remains: "How does one make this information medically useful?". No matter what the outcome may be, discussion and analysis are appropriate. Although the DMB may assist in a technical advisory role, the decision rests with Clinical Center and medical staff of the NIH.

In the area of the Materiel Management System at NIH, the DMB is commissioned to provide an implementation procedure and to work with all areas of the NIH in bringing this system to fruition. The DMB technical plan for this effort extends over a four year period and relies heavily on the NIH administrative service and scientific areas for support. A system of this magnitude requires the total cooperation of all concerned to be successful. Even an outstanding technical effort will fail without it.

II.   PROJECT LIST

The list below does not include a number of small new
projects and modest revisions and additions to existing
systems.   These become literally too   numerous   to
mention in an annual report although each is clearly
important to the client and requires careful work by the
DMB staff.

A.   Clinical Research, Patient Care
     and Epidemiology

1.   Chronic Dialysis Complication Study

The staff of the Artificial Kidney-Chronic   Uremia
program, NIAMDD, is accessing the frequency of various
complications of chronic renal diseases in order to
better direct research efforts to areas of maximum
benefit in improvement of therapy.

To aid in this they have selected five major dialysis
centers, widely scattered over the U.S. and are
reviewing hospitalization records of chronic   renal
failure patients (patients on dialysis) during the year
1976.

We have worked with them in the areas of forms design
and data collection and entry, and have provided a
data base creation and editing facility.   LSMM   is
providing the statistical support for this project.

2.   Patient Record System

The Cardiology Branch, NHLBI, requested a system to aid
them in maintaining records for both in-patients and
out-patients seen by that branch. This will be designed
as a separate system but could possibly interface with
the Cardiac Valve Replacement System in the future.

3. Cardiac Valve Replacement Study Data Processing System

In support of the Clinical Surgery Branch, NHLBI, the DMB developed this system for analysis of the morbidity and mortality of patients who underwent heart valve replacement surgery and to evaluate the various procedures and valves. The analysis for this study is divided into two separate phases. Phase 1, involves the analysis of individual patient profiles following surgery. This includes the progress made from time of surgery to date of last follow up. Phase 2 involves an analysis of the group data accumulated after the first surgery at NIH. It includes such factors as survival rate by type of valve, survival by functional class, survival where embolism is detected and by sex and age of patients to determine the length of survival and the post operative quality of life. In addition the system provides 'on line' retrieval capabilities which serve as an information source for many of the NHLBI investigators.

4. Consultant File Management System

The DMB designed and implemented this system for the Review Branch of Extramural Affairs Division, NHLBI. It provides data on consultants who participate in site visits for projects done under grants and contracts from NHLBI. It includes data pertaining to fields of expertise, history of site visits, etc. The system serves as an aid in forming site visit teams.

5. Sickle Cell Anemia Study

The Molecular Hematology Branch, Division of Intramural Research, NHLBI, is gathering data in the clinical course of the disease in order to predict the course in an individual patient by studying 20-25 sickle cell anemia patients who entered NIH. The desire is for a data entry and retrieval system from which a patient's history can be printed as patients re-enter the hospital, and on which correlations can be run. Additional tests will be added to the data base as they seem relevant.

6. Pulmonary Physiology Report

The Pulmonary Branch, NHLBI, obtains measurements of a patient's pulmonary performance using Collins Lung Analyzers. There are currently two lung analyzers in use. One employs a Data- General minicomputer that produces a printed laboratory report and adds the report to a dataset stored on its own disk pack. The Computer Systems Laboratory (DCRT) is writing a program for this minicomputer which will transmit accumulated reports from the local disk pack to the IBM 370 at DCRT for storage in a Master File. A second lung analyzer produces measurements which are recorded manually. DMB wrote a program under TSO on the IBM 370 to accept these measurements, calculate results, print a laboratory report at the terminal and store the report in an on-line data set. Several programs are to be provided for updating the Master File from this data set and retrieving reports from that Master File.

7. Sleep Studies

This project of the Adult Psychiatry Branch, NIMH, requires that a method be devised that will input and store sleep study data in a format compatable with an existing FORTRAN summarization program. Three programs are needed to reformat and maintain the data file. The first program is complete and ready for production.

8. Cancer Survival System

The Survival System was originally developed by DCRT in the 1960s to support the End Results in Cancer studies of NCI. Maintenance and improvement of the system is the primary goal of DMB.

During FY77 a number of changes were made to the system. The plotting facility was overhauled to reflect changes in DCRT software and hardware. We also sent copies of the software to UCLA, Yale, and Georgetown University.

9. Psychogenetic Studies X-Linkage

The Adult Psychiatry Branch, NIMH, is studying genetic
patterns in families with a history of mental illness.
Specifically under study at this time is the linkage on
the X chromosome between the manic-depressive gene
(location unknown) and the gene for color blindness
(location known). This year a generalized program was
developed to calculate the linkage between two
points on the X-Chromosome by computing LOD scores
(log odds favoring linkage over non-linkage)
corrected for ascertainment and homozygosity.

10. Cutting Oil Study

This supports the efforts of the National Institute of
Occupational Safety and Health in a study relating job
type to mortality and morbidity of cutting oil workers.
During FY77 work was completed on a set of survival or
life table analysis tables.

11. EVIF Medical Records Information System

The EVIF System is a medical records information storage
and retrieval system for the Emergency Virus Isolation
Facility, Viral Oncology Branch, NCI. Its purpose is to
help manage medical and other relevant data kept on EVIF
employees. A serum sample system was developed to help
manage serum samples taken from contract personnel. The
system will interface with the JRB Contract System and
prepare form letters to new contractors informing them
of serum sample requirements.

12. Israeli Diet/Osteoporosis
     Relationship System

The Epidemiology and Field Studies Branch, NIAMDD,
requested DMB assistance in the evaluation of
epidemiologic data on a possible relationship of dietary
intake nutrients to the development of Osteoporosis in
Israeli subjects. The investigator is entering the data
and checking its validity. Programs are being written
for analysis of the data.

13. War Veteran Head Injury Study

The Laboratory of Experimental Neurology, NINCDS, is conducting a restrospective study of Veterans of the Korean and Vietnam wars who sustained head injuries. We were requested to develop a data maintenance and retrieval system. The system has been developed and documented. The user will now be taught how to use it.

14. Clinical Information Utility (CIU)

The CIU is a joint project between DMB's Clinical Support Section and the Office of Clinical and Management Systems in the NIH Clinical Center, to develop a powerful retrieval capability for NIH scientists. The CIU System receives data from the Clinical Lab Computer System, archives it in the NIH Computer Center and retrieves specific subsets on request.

Three new major data bases; Clinical Laboratory Chemistry, Hematology-Bone Marrow and Microbiology were added and now provide retrieval capabilities.

During the coming year several new data bases will be added. These will include Mental Health data, blood bank data, vital signs and x-ray results.

15. Myocardial Infarction Trial Size

More than forty graphs of curve families to be used for predicting the sample size needed for controlled clinical trials with binary end points (e.g. yes or no, death or survival) were produced for the Associate Director of Cardiology, NHLBI.

16. NIAMDD Study of the Incidence and Prevalence of Kidney and Urinary Tract Diseases in the Armed Forces

The study is being conducted to evaluate the occurrences, morbidity and mortality of kidney and urinary tract diseases in an effort to determine research needs. Data for the study was made available by the Air Force, Army and Navy. The Army data was re-submitted to DMB. This has now been edited, reformatted, and new tables were produced.

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17. Adriamycin Toxicity Study

Adriamycin therapy in cancer treatment seems to increase the risk of congestive heart failure. Many factors such as dose level, length of treatment and concomitant therapy must be analyzed to determine whether this suspected relationship is real. In support of this analysis by the Cancer Therapy Evaluation Program, NCI, DMB has designed forms and developed the software to collect data on approximately four thousand patients who are being treated with adriamycin in ten national geographic regions. Analysis of these data is now beginning and will be compared to anticipated European data as it is collected.

B. Laboratory Research

1. Primate Reporting System

Systems are being developed to control data on primates processed through the Veterinary Quarantine Unit Office of the Director, DRS. Programs implemented during FY77 provide for on-line data collection, reformatting, editing of optical scanner output into master record format, updating and editing of the master file and several report programs. Final report programs will be completed during FY78.

2. Mutagenic Testing System

This system will provide programs for the Environmental Biometry Branch of the National Institutes of Environmental Health Sciences to monitor the protocol for mutagenesis testing. Design specifications call for multi-terminal, on-line, conversational program package to interface with laboratory technicians and provide controlled data collection, data storage, and data analysis. This is a pilot project and will be tested under live conditions as part of a current mutagenesis research contract. During FY77, programming continued with a data retrieval capability being added to the system.

3. X-Ray Crystallography System

The University of Maryland supplied the Laboratory of Chemistry, NHLBI, with a set of FORTRAN programs. These were initially converted from CDC equipment to the IBM 370. DMB assistance was requested in compiling and link-editing the programs for use on the DCRT System. Six of the eight major modules contained compiler time errors which were resolved. Systems testing revealed errors in at least six programs. The system is currently undergoing testing of all features and appears to be fully operational.

4. Cancer Tumors in Mice

The Laboratory of Chemical Pharmacology, Division of Cancer Treatment, NCI, has been transplanting human cancer tumors to nude (immunologically defective) mice and treating them with experimental drugs. DMB generated more than 800 separate plots showing the growth rate and shrinkage rate of the tumors, and supplied survival calculations for each experimental group of mice.

5. X-Ray Reconstruction

The Surgical Neurology Branch, NINCDS, requested computer assistance several times during FY77. On the IBM 370 we generated tapes which simulated the EMI (body-scanner) tapes in order to display images on the EMI CRT. On a number of other projects we advised whether or how an application should be computerized.

6. Registry of Experimental Cancers (Tumor Pathology)

Dr. Harold L. Stewart, Registry of Experimental Cancer, NCI, needs a system to handle approximately 23,000 records containing pathology information on mice tissues. Programs for maintaining the file have been completed. IRS (Inquiry & Reporting System) programs have been written for retrieval and printing selected portions of the data.

7. Preselection Methods for Antitumor Chemicals and Drugs

Division of Cancer Treatment, NCI, has a file of structure keys, and a file designating activity or inactivity of 19,000 chemical structures for each of three tumor test systems. Methods of using activity information along with key frequency information to assign priority of compound screening in various test systems, are being explored. The DMB continues to collaborate with Dr. L. Hodes, DCT, NCI, in his study of screening methods and in implementing these ideas for the computer.

C. Program Direction, Management
    and Administration

1. CASE Reports

This annual reporting project for Division of Resources
Analysis,   O.P.P.E.,   summarizes   DHEW   awards   to
institutions of higher education, health professional
schools,   non-profit   hospitals, non-profit research
institutes and operating foundations, and R&E centers.
Data has been received for FY76 and for the transition
quarter. Processing efforts continued on the 1975 data.
DMB has developed a program which will provide an early
warning if a gross difference is found between new year
data and previous submissions.

2. Collaborative Research Project with the
    American Association of Medical
    Colleges (AAMC)

This project for Division of Resources Analysis,
O.P.P.E., combines AAMC data with data from the NIH
Impac System to provide better insights into medical
schools.   It will aid ORA to better interpret CASE
Reports.   It   provides   information   about   grant
applications and review group results (e.g. percent
approved, priority, score, etc.) at the medical school
level.   In addition, DMB also provided a program to
create a Master Roster File which provides
characteristics pertaining to the individual holding an
M.D. degree or combined M.D./Ph.D. (e.g. current fields
of interest, research, etc.).

3. NIH Distribution List System

The Division of Administrative Services, O.D., NIH, has
requested a computerized mailing list system which will
combine the NIH telephone book data with ARMS data.   We
are establishing a data base which will initially
produce a 'check' listing for purposes of establishing
and updating the Current Data File.

4. DRS Activities

The Office of the Director, DRS, asked for a system that will manage the (1) glassware billing system, (2) the small animal billing system and (3) the planning system. The system is fully operational and has been turned over to the Application Program Support Section, DCRT, to be run on a recurring basis.

5. NIH Personnel Accident Reporting System

This system aids the Protection and Safety Management Office, DRS, in the processing and reporting of information about NIH employee accidents along with related information such as corrective measures taken, etc. It will also interface with the DHEW Central Safety System as well as with the Department of Labor system. It is operational; however, a query capability may be added at a later date.

6. Primate Information

The Interagency Primate Steering Committee, Division of Research Services requires quarterly reports from contractors concerning status of animals present in their breeding facilities. Fifteen separate reports were being produced.

We supplied summary programs with edit facilities, and individual run procedures to enable contractors to enter their own data. We also trained personnel and currently are acting as a source of computer expertise for DRS.

7. NIH Library Circulation System

This project is a collaborative effort between CSL and DMB for the Library Branch, Division of Research Services. It involved installing on the NIH/370 System, a Library Control System purchased from the University of South Carolina to receive data from The NIH Library's circulation system, which runs on a PDP-11 computer in the library. Implementing the system required a TSO interface between the NIH/370 and the PDP-11, modifying the JCL, and both changing and rewriting report programs. The system is completely operational and has been turned over to the user. Only a minimum amount of assistance is required from the Data Management Branch.

8. Employee Health Service Data Management System

The NIH Employee Health Service, asked to computerize the collection of information about services provided at the various EHS units. The system is now being operated by the EHS unit and DMB is monitoring it. Some report programs are still to be written.

9. NIDR Program Support

This project for the Office of the Director, NIDR, involves a complete analysis and both programming and re-programming effort for several administrative/ management systems in that office. Areas of consideration include Financial, Contract, Bibliographic and Personnel data. During the year programs to process the contract and personnel data became operational.

10. Cross Reference Supply Lists

The Division of Administrative Services, ODA, maintains computer lists of supplies stored with National Stock Numbers (NSN) and manufacturers part number (FSCM/PN). They were provided with KWIC-indexed listings on microfilm fiche to enable them to search these lists by part name, NSN, or FSCM/PN.

11. Carcinogenesis Bioassay Data System

This system enables the Office of the Associate Scientific Director for Carcinogenesis, NCI, to control the data acquisition, input, purification, reporting and analysis of animal experiment data and the identification of the many agents used in carcinogenesis experiments.

The system is now operational and being run by Mason Corporation under an NCI contract. Modifications are made as needs arise to make the system more useful. Contract personnel are becoming more capable of providing system maintenance. DMB will continue to provide consultation as needed.

12.   The Materiel Management System

The Division of Administrative Services, OA, requested a
system to handle all input, report and output processing
for requisitioning, procurement, inventory, receiving,
property, invoice and payment functions. During FY77,
DMB reviewed the work done previously by two contractors
and devised a revised plan for implementation of the
system. The concept under which implementation will
begin is to provide interactive terminal input and
retrieval functions with message outputs to other
systems and detail and summary reports as the data base
expands.

The initial implementation will accept input from both
central and delegated procurement areas, provide
obligation information to the Central Accounting system,
write an SF-147 Purchase Order for each central
procurement, provide an order report for the Division of
Financial Management on all procurements and prepare a
weekly order summary list for the administrative areas
within the B/I/D's. In addition, the "Vendor" programs
will be upgraded to allow for better control over the
input procedure, to expand the data elements where
necessary, to provide a method for linking old vendor
numbers to new and for appending a date of last order to
each vendor for later review and purge consideration.
The schedule calls for implementation in early January,
1978.

13.   NCI/DCT Budget Analysis

The Division of Cancer Treatment, NCI, maintains a data
set consisting of cost information on Clinical Trials
and Preclinical screening of drugs. This involves
contract data and is now being expanded to include
grants data as well. Seven programs for maintaining the
file, in addition to producing reports, were completed
by DMB. The system is now operational and being run on
a production basis by NCI/DCT.

14. NIH International Activities and Personnel Monitoring System

This system provides the Fogarty International Center with the capability to maintain and query a data base covering the following:

1. Visiting Scientists, Associates and Fellows

2. Foreign Guest Workers of NIH

3. Foreign Visitors at NIH

During the year, the system was expanded and now provides both financial data and visa data. Special query capabilities are to be provided throughout the year as needs are defined.

15. Computerized RAEB Grants Information Files

This system developed for the Division of Cancer Grants, NCI, satisfies a need in the Research Analysis Evaluation Branch by providing automated information files. These provide ease of maintenance, reduction in cost and detailed retrieval of extramural funded grants data. Programming is underway for intramurally funded grants which will be similiar but will interface with the CRISP system rather than with IMPAC. Basically the same system(s) is being used for 'Unfunded Grants' which are a separate file.

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D. Biomedical Communications

1. Selective Dissemination of Information (SDI)

The current awareness tapes of Chemical and Biological
Activities (CBAC) provided on a biweekly basis by
Chemical Abstracts Service, are compared to profiles of
researcher interest. All relevant literature abstracts
are disseminated to individual research investigators as
they are identified. This current awareness facility is
provided free to all NIH investigators upon request.

In addition DMB provides similar support of the
current awareness search of Biosciences Information
System (BIOSIS). Twice a month tapes are received
from the Biological Abstracts Service.

Several changes were made to the output format during
FY77 including addition of the notification of lease
terms as required by our lease. Consideration is being
given to the possibility of requesting that additional
sections of Chemical Abstracts be added to our tape.
The outcome of this may depend on an analysis of the
increase in lease cost and in processing costs.

2. Journal of the NCI (JNCI) Computer System

The Division of Cancer Cause and Prevention, NCI, is
responsible for producing the JNCI. This is a monthly
medical journal consisting of approximately 900
manuscripts per year. The computerized system aids in
the handling and processing of much of the data
submitted for publication in the Journal. A generated
update to the system is completed. A Wylbur input mode
for data entry is operational and a report program for
manuscript file display has been written. Another
program which will produce an Author Index on microfiche
is also complete.

3. The National Clearinghouse for Capacity
Building and Human Services
Integration Program

The Clearinghouse service is being provided by the Aspen
Systems Corporation under a DHEW contract. In support
of this effort the DMB developed a system of programs to
collect, update, query and print the file of subscribers
to the service. A program to print abstracts for the
Journal of Human Services publication is now
operational.

E. Tools for Data Management and Analysis

1. Inquiry and Reporting System (IRS)

IRS is a proprietary package developed by Sigma Data Corporation. During FY77 DMB continued its user support of this system. This includes maintaining the integrity of IRS by testing new IRS releases and notifying users of changes to IRS, keeping informed about DCRT hardware/software changes that may affect the operation of IRS, and providing IRS classes.

2. Recursive Macro-Actuated Generator
   (RMAG Project)

RMAG is a programming language used for the generation of other source programming languages and Data/Text strings. The original RMAG was implemented in 1970 as a compiler, i.e. a program that functioned in the main batch job stream of the NIH Computer Center, reading programs written in RMAG langauge and generating specific programs for users. Since its implementation several very powerful additional arithmetic and logical features were built into it, but its mode of access and use as a compiler remain the same.

In FY77 the three previously developed subroutine callable packages

(1) RMAG22,
(2) the Logic Subroutines, and
(3) the Arithmetic Subroutine

were extensively used in the development of a powerful, sophisticated information retrieval system. In the process the subroutine callable packages themselves were improved. The new information retrieval system is known as SLR (for Symbolic Logic Retrieval). An RMAG22 encoded generator, reading free form specifications of the user's file structure, generates a customized COBOL program which interactively retrieves selected records from the user's file. The generated COBOL program permits its user to interactively utilize sentential calculus selection schemata, implied existential quantifiers, sophisticated arithmetic specification, the RMAG22 macrogenerator, and external macro libraries. Because RMAG22 has been made a part of it, the user's generated SLR is extensible at any time in the future without the need to then modify the source program.

Also in FY77 another new Project RMAG product has been
developed. Known as REPORTGEN, this product is an
RMAG22 encoded generator for producing customized COBOL
programs which create highly versatile reports from the
user's data utilizing the Report Writer feature of
COBOL.

This product involved development of a special purpose
high-level programming language for routine operations
on data files. Programs can now be generated (a) to
create and update files using key oriented transactions,
(b) to reformat data files, and (c) to index textual
data from files (file inversion). Files are assumed to
have, in general, multiple logical records per subject.
Any generated program can validate or error-check data
in the files it reads, using conditions involving
relations between fields. This year's efforts centered
around the following (1) providing systems documentation
for using the system (2) improving it and (3) providing
user support to users of the system.

3.   Unified Generator Package

A unified set of generators has been designed and
implemented in RMAG22. The Generated programs are in
360/370 assembly language except for the reformatting
routines, which are in COBOL using the Report Writer
feature. All features of the system which include
updating, reformatting and reporting procedures, and
selection and validation capabilities are essentially
complete and have been made available for use. Work
continues in improvements to the overall package and
'user' documentation is being finalized.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities   1.   <u>DCRT</u>

2.   <u>Computer Center Branch</u>   3.   <u>Joseph D. Naughton</u>
                                              Chief

I.   SUMMARY

<u>Function</u>

The Computer Center Branch was established to provide efficient
and effective central computational services for the NIH on a
fee-for-service basis under the NIH Service and Supply Fund. The
objective of the Computer Center is to incorporate proven
advances in computer technology into a reliable, accessible,
economic Computer Utility to support NIH scientific and
managerial programs. The need to preserve the integrity of data
and insure the integrity of computing is its primary concern.
Its challenge is to achieve new improvements while maintaining
the quality of service to science and its management at NIH.

The main concern of users of the Computer Center is "How can I
use the computer to better accomplish my job?" and once using the
system, "How fast can I get my results?" Additions or
improvements are needed continuously to maintain the
responsiveness of the Utility and to provide services consistent
with the rapidly changing state-of-the-art of computing.

<u>Activities</u>

The NIH Computer Center designs, implements, and operates a
powerful network of modern computers and communication
facilities. The nucleus is composed of two large multi-computer
subsystems, the IBM 370 system and the DEC-10 system, each having
unique capabilities. Communications facilities link these two
subsystems and connect them by telephone lines to over a thousand
remotely located terminals of various types. The computing and
communications equipment (systems hardware) are controlled,
balanced and complemented by a very complex set of computer
programs (systems software) designed and implemented by the
Center or acquired from other sources and adapted to meet unique
NIH needs.

Services and facilities provided by the Center include standard
programming languages (e.g., FORTRAN, COBOL, PL/I, SAIL, Assembly

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Language), a data base/data management system (IMS), and a large and varied library of utility programs. For users with terminals there are also interactive systems such as WYLBUR, TSO, and the DEC time-sharing system, whcih facilitate creation, submission and output of jobs and permit direct interactive computing (using FORTRAN, BASIC, CPS, APL, MLAB and other languages). The Center also contains a variety of facilities for output of printed material or graphics on paper and microfiche. Programs to show two or three dimensional pictures on cathode ray tube displays and "sketch pads" for advanced graphic projects such as those examining macro molecular structures are also available.

In addition, the Center provides extensive training, technical documentation, information services and assistance with problem diagnosis for its users. It also offers limited sources for data entry and recurring program maintenance and production.

Scope of Work

The Computer Center operates the NIH Computer Utility 24 hours a day, for over 5,000 users, including people from all NIH Bureaus, Institutes, Divisions and Offices.

IBM System 370 Facility: During FY77, the workload handled by this facility grew 21% over the previous year. (Figure one is a chart of workload growth since 1967.) At year's end, the Center was handling over 340,000 tasks per month. This number includes 8,000 mainstream jobs a day processed by the utility, with 80% of them completed within one hour. Interactive timesharing sessions via remote terminals have risen to over 4,000 a day.

DECsystem-10 Facility: The level of activity on the DECsystem-10 reached an all-time high since it began a fee-for-service operation in July 1972. The number of user sessions grew to over 10,000 per month, the amount of terminal connect time now exceeds 12,000 hours per month while CPU utilization exceeds 320 hours per month. Finally, a very important indicator of the growing recognition of the DECsystem-10 as a valuable adjunct to the Computer Center's facilities is that the number of registered DECsystem-10 users reached 1,000 this year.

Manpower: Only a small part (about 12%) of the operating expenses of the Computer Center are personnel costs, but those 132 people are the absolutely essential ingredient in the Center's success in support of computing at NIH. About two thirds of them have responsibility at a daily operating level to insure that work is ready for and completed in a timely fashion within the Computer Utility. The other third are responsible for maintaining the integrity of the complex hardware and software systems, educating and assisting users and developing new services and facilities. While the overall workload of the Computer Center increased 21% in FY 1977, the number of people available to do the work was reduced by over 10%.

Highlights of this years activities

FY77 was the 10th consecutive year that the Computer Center provided NIH with planned improvements to existing services; added new facilities and reduced its rates to users. Two major operating systems were upgraded, improvements were made in graphics, printing and communication's facilities, and users received the benefit of rate reductions that totaled nearly 25%.

Upgrading of Systems

.System upgrade: IBM 370. A major activity of the Computer Center was the transition to the new, more powerful Multiple Virtual Storage (MVS) Operating System. Over two years of continuous effort in the implementation and testing of the new MVS operating system came to an end as the switch from OS/MVT became final in March. To meet the requirements of NIH computer users all functions available under the old system were made available under the new system without requiring modification of users' programs or data files.

There were three phases of implementation and testing to prevent interruption in on-going production service during the transition period and to insure a level of system performance and reliability adequate to meet the stringent requirements of the NIH Computer Utility. Phase 1 saw the users testing both TSO and batch under MVS. In phase 2, TSO went into production while batch testing continued. During phase 2 several free test days of the whole system under MVS for full load user testing were offered. Finally phase 3 was completed in March as the whole installation was in full production operating under the new MVS operating system.

MVT-MVS Bridge. A notable accomplishment of the MVS transition was the design and implementation of a software "bridge" between the old MVT operating system and the new MVS operating systems. This "bridge" permitted the two operating systems to transmit jobs, data sets, and status information dynamically between the two operating systems. It was the "bridge" that allowed the switch to be made in three phases to minimize disruption to user projects. Using the "bridge", for example, a user on WYLBUR in the MVT environment could submit a job and have it transmitted to the MVS machine, executed there, and returned to the MVT system for fetching or printing or other necessary action. Likewise, users on TSO under MVS could send jobs and output to the MVT system over the bridge. This intercommunications tool was a critical factor in enabling the Computer Center and its users to test the MVS system thoroughly. The stability and reliability of the new system is ample evidence of the thoroughness of the testing that was provided by development of the bridge.

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Furthermore, the bridge concept, conceived and developed by the NIH staff, was a technical breakthrough which even the manufacturer's systems software experts had declined to attempt.

.DEC-10/IBM 370 Link. A major milestone was reached when the DECsystem-10 and the IBM 370 were linked. This link, called MERCURY, enables users to automatically transfer data files and jobs between the two major components of the NIH Computer Utility. DECsystem-10 users can now avail themselves of the large volume printing services of SPOUT, and the data handling power of the IBM 370. Likewise, the 370 users can avail themselves of the interactive graphics and timesharing facilities of the DEC-10.

Services and Facilities

.DEC-10 Improvements. DEC-10 users benefitted from the introduction of new hardware and software. New terminals, both hardcopy and CRT were installed in the user area. Online plotting speed was increased with the installation of a 1200 baud Zeta plotter. A program called DIGIT was introduction to convert XY coordinates from plots into input files for MLAB. The amount of virtual memory for DECsystem-10 users was increased 25% to 512 pages. Users could avail themselves of more DECsystem-10 time as unattended service was extended to cover the entire weekend.

.370 Improvements. The installation of the new MVS Operating System permitted the Computer Center to move forward, providing both increased resources for existing services and the development of new facilities not possible under the old operating system. Most significant to users were major increases in standard job class limits. The maximum amount of memory permitted for job classes A, B and C was increased from 300K to 500K and class H was increased a full 150%. In addition, class H jobs now receive overnight service.

Remote Job Entry (RJE) users realized additional benefits from the transition to MVS. For the first time, RJE workstations could print output in both upper and lower case, handle special printer forms and transfer information on magnetic tape to and from the Computer Utility. The data transmission speed of the RJE dial-up network was upgraded from 2000 baud to 4800 baud. Thus, output to these terminals is significantly faster.

The maximum number of lines which can be printed online was increased from 20 to 50 thousand for all job classes, and two "special" printing forms, previously only available offline, were

made available to all job classes online. These increases permitted users to optimize existing programs to improve efficiency and to develop new applications which were not possible under the old limits.

A new plotting package, IPP, replaced the IGS package. This new package made the transition to the newly installed CALCOMP plotter a smooth one.

The RFP for the new CRT terminals finally met with GSA approval and these may be available to users soon. As the year came to an end, a new laser type printer was installed. It produces high quality printed output three to five times faster than the old printers and helps get output back to users more promptly. A new feature of that new printer provides for 132 column output on 8X11 inch paper. Thus, a savings in paper used is realized and much more convenient size of printer output is produced for users.

.Molecular Structure Atlas. The Atlas of Macromolecular Structure on Microfiche (AMSOM) was developed over the last three years using the facilities of the DECsystem-10 and the microfiche facility of the IBM 370 System. The atlas permits scientists to have the capability of studying the configuration of macromolecules in three dimensions at a very low cost. The atlas is now in use at universities and research institutions all over the world.

.Rate Reductions. Two rate reductions totalling nearly 25% were put into effect during the year. The first 11% became effective in December. After the transition to the MVS was complete and the Center was able to evaluate the overall effect of the new operating system, another rate reduction of approximately 15% was offered for System 370 services in May. Thus, the cost of computing decreased significantly and users were able to do much more computing than they budgeted for.

User Education and Assistance

A crucial factor in the effectiveness of any computer center is aid to its users in learning how to use its facilities effectively and in overcoming any problems they encounter. For the ninth successive year the Computer Center organized both a fall and spring term of Computer Training Courses and Seminars. Sixty-one courses provided training at all levels to over 1300 students. These courses covered an entire range of general purpose programming languages, special services and facilities, programming aides, job control languages, use of statistical and mathematical packages (BMD, SAS, SPSS, PSTAT, MLAB, MODELAIDE), query and reporting facilities (IRS), and programming tools (RMAG

21, PDP-11 tools). Ten seminars taught by DCRT mathematicians and scientists covered such diverse topics as laboratory computers, time series analysis, Macro molecule ligand binding models, pattern recognition, diffusion and biophysical techniques.

The Programming Assistance and Liaison (PAL) unit received more than 10,000 personal or telephone requests for assistance and analyzed some 3,400 written Programmer Trouble Reports (PTRs). Equally important, the Center helped its users avoid many problems. Its Technical Information Office used its automated files to insure that all users received new or revised copies of any manuals they had previously received. The Center published and distributed five issues of INTERFACE, its technical notes covering new services, facilities, procedures, diagnostics and hints as well as recognized "bugs" and ways to avoid them.

Overall the Technical Information Office stocked and distributed some 60,000 pieces of documentation to over 3,000 users, including technical reference manuals and guides and the Computer Center Users Guide. Both the Users Guide and the Timesharing Guide were completely rewritten and many technical reference manuals were revised extensively.

Future Plans

Completion of the MVS conversion has put the Computer Center back on a more normal path. The Center is currently faced with shortages in several areas, online disk space, air conditioning and electrical power. Contracts have been let to improve the physical plant to provide necessary utility services and to improve security of the Computer Center and the data it handles. Vitally needed improvements - online disk space are dependent on receiving GSA's blessing.

As the year came to an end, the long awaited Building 12B was completed. The move of some of the Computer Center staff into it will enable both the second floor of Building 12 and the first floor of 12A to be remodeled. This will provide additional computer space to house the DEC-10 and new equipment in Building 12 and will enable all user-oriented facilities to be located together on the first floor of Building 12A. Locked user output boxes (comparable to post office boxes) and a computerized access control system will be installed to provide better separation of the computer area from public areas and to protect personal data as required under the Privacy Act of 1974.

The hardware for a system for the display of line drawings and shaded surfaces is being installed. This equipment will have the capability of replacing the existing AGT-30 and the DEC-340

displays. As part of the initial development, the new display system will provide graphic support for the modeling of macromolecules from electron density maps. The raster display which is part of this system will permit the same objects to be represented as shaded and colored surfaces. Other molecular assemblies and the interaction of proteins with membrane surfaces can be modeled with the same system.

New WYLBUR, a completely redesigned version of the Center's most popular interactive system, is under system test. The system will be available to users in the coming year providing them with more powerful editing and macro capabilities.

Data storage is a continuing problem as NIH research programs expand to include more and more research and patient care data. The tape library has overflowed its space many times over and online disk space is a constant problem. The future should see the introduction of a new type of Mass Storage Unit. Such a unit could store extemely large amounts of data in a relatively small space. All the data stored on it is transferrable in a matter of seconds to online disk units where it is directly accessible by the main processor. Plans to upgrade online disks are well underway. The new units will enable the Center to increase its online storage capacity almost four-fold. The new units will also provide a higher data transfer rate and improved reliability.

Changes in technology together with NIH program requirements for increased computational capacity and new function require that major components of the NIH Computer Utility be replaced by new more cost effective units. In addition to new faster processors and disk drives with larger storage capacity for both the System 370 and the DECsystem-10 facilities, and a mass storage system, improvements are already long overdue for tape drives, communication controllers and both interactive and batch remote terminals of all types. Unfortunately, constant contention with GSA over every improvement that NIH has attempted in the past few years has prevented upgrading the present equipment to keep abreast of the changing needs of the NIH research program. The principal problem has been GSA's unwillingness to recognize the efficiency and effectiveness of continuing development within the same family of equipment. The cost in manpower, dollars and lost time and opportunity of converting to another manufacturer's equipment would not only be disastrous to NIH research programs but would be wasteful of the tremendous investment which NIH had made in its Computer Utility over the past ten years. The success of providing responsive cost effective computer support to a dynamic research program, such as NIHs, depends on fast straight forward procurement of the proper equipment at the right time. If the pertinacious discussions with GSA of the past continue, it will be impossible to predict if or when the equipment necessary to provide proper support to the NIH biomedical research and management program will be available.

PERIOD COVERED
July 1, 1976 - September 30, 1977

TITLE OF PROJECT (80 characters or less)
Graphic System for the Display of
Biochemical and Biomedical Objects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Richard J. Feldmann, CCB, DCRT, Computer Specialist

Others: Thomas K. Porter, CCB, DCRT, Computer Specialist
        Charles R. T. Bacon, CCB, DCRT, Computer Specialist

COOPERATING UNITS (if any)

None

LAB/BRANCH
Computer Center Branch

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bldg., 12, Room 3009, Bethesda, MD 20014

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.5	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☐ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A new graphics facility is being implemented with the goal
of presenting biochemical and biomedical objects either as
line drawings or shaded surfaces. An Evans and Sutherland
Picture System with a frame Buffer and Camera Station is
interfaced to a DEC PDP-11/70 which is in turn interfaced to
the DECsystem-10. Users will be able to generate image data
using either the PDP-11 or the DECsystem-10. A standard
pathway from existing programs on DECsystem-10 to the
Picture System will provide for the bulk of the low level
use. Programs for special forms of graphic interaction and
graphic computation in the PDP-11 will permit higher
level users to structure the system to solve specific
problems.

PHS 6040

Graphic System for the Display of
Biochemical and Biomedical Objects

Consideration has been given to the choice of lauguage   for
the   PDP-11.   The   choice   has been narrowed to MAINSAIL, a
machine independent ALGOL   and   PASCAL.   Implementation   of
both   languages   for   the operating system of the PDP-11 are
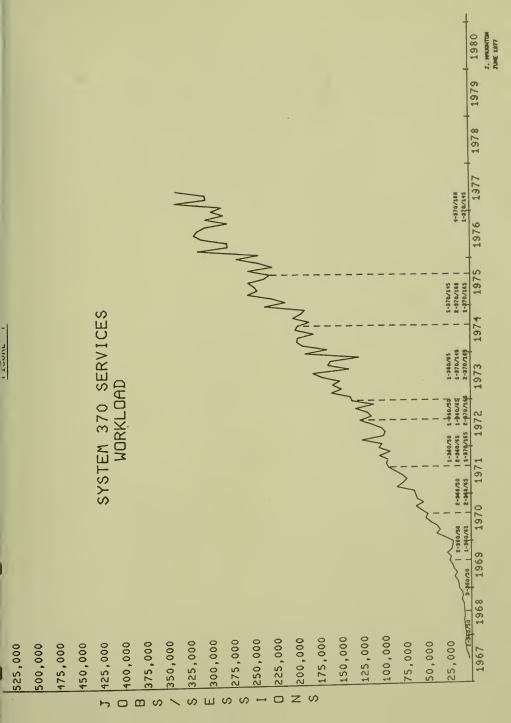currently being done at other institutions.

PERIOD COVERED
July 1, 1976 - June 30, 1977

TITLE OF PROJECT (80 characters or less)

Atlas of Macromolecular Structure on Microfiche (AMSOM)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Richard J. Feldmann, CCB, DCRT, Computer Specialist

Other: R.L. Tate, Ph.D., CSL, DCRT, Senior Staff Fellow

COOPERATING UNITS (if any)

Department of Chemistry, Brookhaven National Laboratory

LAB/BRANCH
Computer Center Branch

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DCRT, NIH, Bldg., 12A, Room 3009, Bethesda, MD 20014

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.5	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS   ☐ (b) HUMAN TISSUES   ☐ (c) NEITHER

☐ (a1) MINORS   ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Atlas of Macromolecular Structure on Microfiche (AMSOM) was published in March of 1977. About 100 copies are now being used by scientists all over the world. Each copy consists of an index volume which directs the user to the 650 microfiche and a stereo box with its related pair of stereo glasses. Because any microfiche viewer can be used the scientist population to which AMSOM was directed has had little trouble getting down to serious use. Early reports indicate that AMSOM will be heavily used to make systematic studies of the environmental contexts of various amino acids as well as the variations in the configuration of secondary structure units (alpha helices and beta sheets).

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(Rev. 10-76)

Atlas of Macromolecular Structure on Microfiche

Preparation of the first supplement is under way with about 40 new structure states available. A structure state suitable for inclusion in the supplement can be either a new structure or a refinement of a structure included in the first edition of the atlas. In addition, the scope of the atlas has been expanded to include small circular polypeptides and a new class of theoretically determined structures. Over seventy new crystal structure studies have been identified for the supplement. The supplement should be the same size as the first edition when it is published in 1978. This conforms with the expected exponential rate of increase of both new structure states and new crystallization studies.
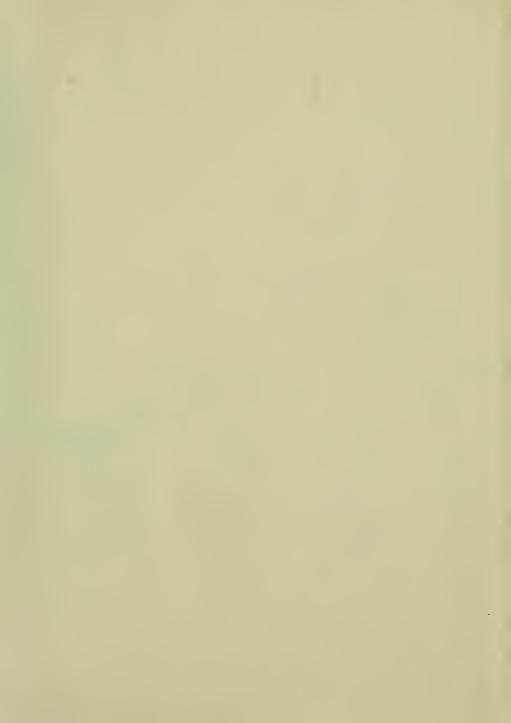
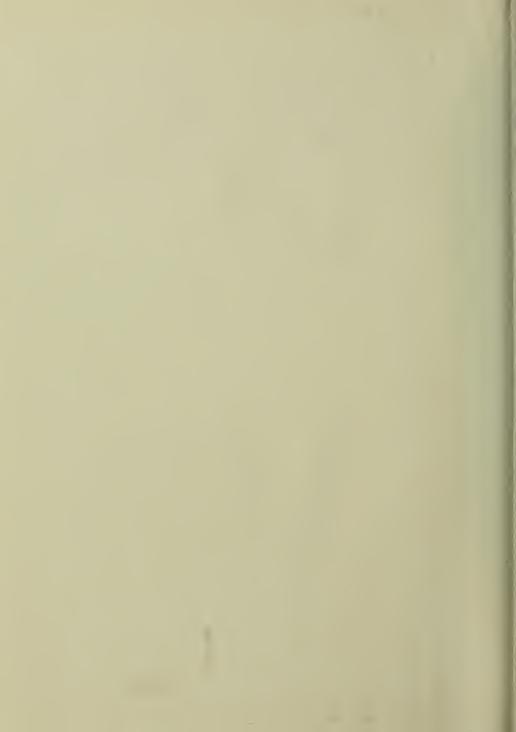Keyword Descriptions: Macromolecular structure, microfiche

SYSTEM 370 SERVICES
WORKLOAD

J. NAUGHTON
JUNE 1977